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A quantitative description of solute and fluid transport during peritoneal dialysis

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A quantitative description of solute and fluid transport during peritoneal dialysis. To investigate the relationship between dialysate glucose concentration and peritoneal fluid and solute transport parameters, 41 six-hour single dwell studies with standard glucose-based dialysis fluids containing 1.36% ($N = 9$), 2.27% ($N = 9$) and 3.86% ($N = 23$) anhydrous glucose were carried out in 33 clinically-stable continuous ambulatory peritoneal dialysis (CAPD) patients. Intraperitoneal dialysate volumes (V_D) were determined from the dilution of ^{131}I-albumin with a correction applied for its elimination from the peritoneal cavity (K_E, ml/min). Diffusive mass transport coefficients (K_{BD}) were calculated from aqueous solute concentrations (with a correction applied for the plasma protein concentration and, for electrolytes, also for the Donnan factor) during a period of dialysate isovolemia. The intraperitoneal amount calculated to be transported by diffusion was subtracted from the measured total amount of solutes in the dialysate, yielding an estimate of non-diffusive solute transport. The intraperitoneal dialysate volume over time curve was characterized by: initial net ultrafiltration (lasting on average 92 min, 160 min and 197 min and with maximum mean net ultrafiltration rates 6 ml/min, 8 ml/min and 14 ml/min, respectively, for the 1.36%, 2.27% and 3.86% solutions); dialysate isovolemia (lasting about 120 min for all three solutions) and fluid reabsorption (rate about 1 ml/min for all three solutions). K_{BD} for glucose, potassium, creatinine, urea and total protein did not differ between the three solutions and the fractional absorption of glucose was almost identical for the three glucose solutions, indicating that the diffusive transport properties of the peritoneum is not influenced by the initial concentration of glucose or the ultrafiltration flow rate. About 50% of the total absorption of glucose occurred during the first 90 minutes of the dwell. The mean percentage of the initial amount of glucose which had been absorbed (%GA) at time t during the dwell could be described ($r = 0.999$) for all three solutions using the experimental formula $\%GA = 85 - 75.7 * e^{-0.005*t}$. After 360 minutes, about 75% of the initial intraperitoneal glucose amount had been absorbed corresponding to a mean (± SD) energy supply of 75 ± 6 kcal, 131 ± 18 kcal and 211 ± 26 kcal for the three solutions. Non-diffusive (that is, mainly convective) transport was almost negligible for the less hypertonic solutions while it was estimated to account for 30 to 40% of the total peritoneal transport of urea, creatinine and potassium during the first 60 minutes of the 3.86% exchange.

Glucose is still the most widely used osmotic agent for peritoneal dialysis, although alternative osmotic agents such as glycerol [1, 2], amino acids [3, 4] and glucose polymers [5] have been investigated in small groups of patients. Three standard glucose solutions containing 1.36%, 2.27% and 3.86% of anhydrous dextrose/glucose are used in the majority of continuous ambulatory peritoneal dialysis (CAPD) patients. Despite the widespread use of glucose-based solutions, peritoneal solute and fluid transport characteristics are still not well described for standard dialysis solutions in CAPD. A detailed quantitative analysis of fluid and solute transport parameters for these solutions is of value for the clinical management of CAPD patients using current solutions, as well as for the evaluation of changes in treatment strategies such as the introduction of new osmotic agents.

During peritoneal dialysis solutes are transported through the peritoneal barrier both by diffusion (due to the concentration gradient between blood and dialysate) and by convection (due to the osmotic dysequilibrium caused by the osmotic agent). Diffusion is the main transport mechanism [6] although the use of hypertonic dialysis solutions may result in substantial convective transport [6, 7]. However, the relative importance of diffusive and convective transport for different solutions has as yet not been established in detail. A variety of models based on the theory of transport across the homogeneous membrane are available for the mathematical description of the diffusive and convective components of peritoneal transport [6, 8–13]. However, the determination of the convective component using these models is associated with difficulties in the physiological interpretation of the convective transport parameter, sieving coefficient, which has been found to be outside the physiological acceptable range for several investigated small solutes [12].

We have previously applied an alternative method (isovolumetric method) to evaluate the diffusive transport parameter [2, 3, 12, 14]. An advantage with this method, which was applied in the current study, is that it does not require any assumptions concerning the theoretical description of convective peritoneal transport [2, 3, 12, 14]. However, it should be noted that dialysate isovolemia indicates zero ultrafiltration through the peritoneal membrane only under the premises that lymphatic absorption and recirculation of water between blood and dialysate are negligible.

The continuous glucose absorption from the dialysate during CAPD treatment (with a positive glucose gradient existing even after a dwell time of six hours with 1.36% glucose solution [15]) results in a unique metabolic situation in which the patient is never in a true fasting state. This is of importance for the nutritional status of the patients since glucose absorption may

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Table 1. Patient characteristics for three groups of patients undergoing single dwell studies with 1.36%, 2.27% and 3.86% glucose dialysis solution, respectively

	N	Age *years*	T_{CAPD} *months*	Body wt *kg*	PIT *N*	V_U *ml/24 hr*	Diagnosis			
							CGN	IN	PKD	Other
1.36%	9	61 ± 8	26 ± 19	62 ± 10	1.3 ± 1.2	117 ± 277	3	2	3	1
2.27%	9	60 ± 7	23 ± 14	63 ± 11	1.7 ± 3.2	157 ± 190	3	2	4	—
3.86%	23	57 ± 12	16 ± 17	66 ± 15	1.3 ± 2.9	151 ± 262	12	5	2	4

Data are means ± SD. Abbreviations are: T_{CAPD}, time on CAPD treatment; PIT, number of previous peritonitis episodes; V_U, urine volume; CGN, chronic glomerulonephritis; IN, interstitial nephritis/chronic pyelonephritis; PKD, polycystic kidney disease. Statistical analysis (ANOVA) showed no significant difference between the three groups.

serve as an important source of energy. However, glucose absorption may also contribute to adverse metabolic effects such as hyperlipidemia, hyperglycemia, hyperinsulinemia and obesity [16, 17]. Thus, studies on peritoneal glucose transport are of importance for the investigation of metabolic effects of CAPD.

The aim of this study was to evaluate peritoneal solute and fluid transport for the three most widely used, standard glucose-based solutions in order to characterize differences in fluid transport patterns and to assess the possible influence of different dialysate glucose concentrations on diffusive mass transport coefficients. The isovolumetric method, which is based on the assumption that the impact of convective solute transport during dialysate isovolemia is negligible, is not directly applicable to assess convective solute transport. Therefore, to quantitatively assess the relative importance of diffusive versus non-diffusive peritoneal transport of solutes, the total amount of solutes transported to the dialysate was measured and compared with the calculated amount that would have been transported if diffusion had been the only transport mechanism.

Methods

Patients

A total of 41 six-hour dwell studies, with standard dialysis fluid containing glucose as osmotic agent (anhydrous glucose of 1.36%, 2.27% and 3.86%, respectively) were performed in 33 CAPD patients using a uniform study protocol (see below). Note that the concentrations correspond to 1.5%, 2.5% and 4.25% hydrous glucose, respectively, as the solutions usually are quoted in the United States. Nine patients were studied with 1.36% glucose dialysis fluid, nine patients with 2.27% glucose dialysis fluid and 23 patients with 3.86% glucose dialysis fluid. Two patients were studied with all three glucose concentrations, four patients were studied with two different concentrations and 27 patients were studied with one of the solutions. The dwell studies were made as part of the routine clinical follow-up of the patients or as part of studies of alternative osmotic agents [2, 3].

The clinical characteristics of the patients and the etiology of endstage renal disease are given in Table 1. None of the patients had diabetes mellitus, or vascular disease such as vasculitis known to influence capillary transport. The patients had minimal residual renal function (Table 1) and had been treated with CAPD for 0.5 to 65 months prior to the study. None of the patients had been treated with recombinant human erythropoietin, and their mean ± SD hemoglobin level was 95 ± 17 g/liter. All patients had been free from peritonitis for at least one month prior to the study. Sixteen patients had had no peritonitis episodes and in the other 17 patients the peritonitis free interval before the study was 1 to 32 months. A small but statistically significant difference in the diffusive mass transport coefficient, K_{BD}, was seen between the patients with and without previous peritonitis episodes (**Results**). All patients were in a clinically stable condition with no signs of impaired peritoneal ultrafiltration capacity.

Dialysis technique

CAPD was performed according to standard methods using glucose-based solutions with lactate as a buffer [18]. During the week preceding the study, the patients used a mean number of 3.9 exchanges per day; the average ± SD glucose concentration used (calculated as the total amount of glucose in the bags per day divided by the total volume of dialysis fluid instilled per day) did not differ between the three groups (2.40 ± 0.43 mg/ml, 2.31 ± 0.30 mg/ml, and 2.43 ± 0.37 mg/ml for the 1.36%, 2.27% and 3.86% solution groups, respectively).

Study protocol

The six-hour dwell study was carried out with 2 liters of glucose 1.36%, 2.27% or 3.86% dialysis fluid (Dianeal, Baxter-Travenol, Deerfield, Illinois, USA or Halden, Norway) supplied in plastic bags (Viaflex, Baxter-Travenol). The electrolyte and buffer concentrations were: sodium 132, calcium 1.75, magnesium 0.75, chloride 102, and lactate 35, all in mmol/liter. The measured glucose concentration in the fresh dialysis fluid was 73 ± 3 mmol/liter, 121 ± 5 mmol/liter and 209 ± 6 mmol/liter for the 1.36%, 2.27% and 3.86% solution, respectively. The total osmolality of the dialysate was 334 ± 6 mOsmol/kg, 380 ± 10 mOsmol/kg and 479 ± 6 mOsmol/kg for the three solutions, respectively.

The patients were studied in the morning after an overnight oral fast. Overnight dialysate, which was instilled at about 10:00 p.m. in the evening before the study (Dianeal glucose 1.36% in all except two cases in which Dianeal glucose 2.27% was used) was drained at 7:15 a.m. Fresh dialysis fluid (Dianeal glucose 1.36%, 2.27% or 3.86%) was prewarmed to 37°C and prepared with a priming dose of 0.2 g of human serum albumin to minimize the adhesion of the tagged albumin to the surface of the plastic material. Radioisotopically labelled albumin [185 kBq ^{131}I-human serum albumin (RISA), Institutt for Energiteknikk, Kjeller, Norway] was added and the fluid was then infused through an infusion set (CAPD Solution Transfer-set, Travenol Laboratories). Fresh dialysis fluid samples were taken

from the bag halfway through infusion. Dialysate samples (15 ml) were taken through a three-way stop-cock (Viggo, Connecta, Helsingborg, Sweden) and an indwelling permanent Tenckhoff catheter at 3, 15, 30, 60, 90, 120, 180, 240, and 360 minutes after the complete infusion of the dialysis fluid. Prior to each sampling, 10 ml of the dialysate was flushed back and forth five times through the stop-cock. Blood samples were drawn at 0, 180 and 360 minutes (0, 30, 60, 180, 240, and 360 min for determination of glucose in most patients). After 360 minutes, the dialysate was drained and the volume recorded. The peritoneal cavity was then rinsed for five minutes with 1 liter of fresh 1.36% glucose dialysis fluid (without RISA) to provide data for calculation of the residual volume at 360 minutes.

The volume of the infused fresh dialysis fluid and the drained dialysate were measured by weighing the bag and subtracting the weight of the empty bag. Corrections for differences in the specific weight of the solutions were not carried out.

The patients were instructed to sit up or to move about in bed before each sampling of dialysate; otherwise they were recumbent throughout the six hour investigation. Informed consent was obtained from each patient, and the study was approved by the Ethical Committee of the Karolinska Institute at Huddinge University Hospital.

Analytical methods

Blood and dialysate samples were analyzed for RISA activity on an Intertechnique CG Gamma Counter (Intertechnique, Plaisir, France). Glucose, urea, creatinine, and total protein concentrations were measured with an IL 919 system (Instrumentation Laboratory, Milan, Italy), sodium and potassium concentrations with an IL 743 flame photometer (Instrumentation Laboratory), and osmolality on a Wescor vapor pressure osmometer (Wescor Inc., Logan, UT, USA).

Calculations

Intraperitoneal dialysate volumes (V_D) and net ultrafiltration rates were estimated from the dilution of RISA with corrections applied for the elimination rate of RISA from the peritoneal cavity (K_E, ml/min) and sample volumes [2, 3, 14, 19]. The diffusive mass transport coefficient (K_{BD}) was calculated using a one hour period of dialysate isovolemia [2, 3, 14]. The calculation of K_{BD}-values were performed using the aqueous concentration of the investigated solutes in plasma water, C_{PW} [20]. C_{PW} was calculated from the measured whole plasma concentration of investigated solutes (plasma concentration), C_{BP}, corrected for the plasma total protein concentration according to the following formula [20, 21]:

$$C_{PW} = u \cdot C_{BP}, \quad u = 1/(0.984 - 0.000718 \cdot C_{prot}) \quad (1)$$

where C_{prot} is plasma total protein concentration in g/liter. In this study, the time averaged value of plasma total protein concentration during the dwell study was taken as C_{prot}. In the dialysate, the corresponding correction for the measured concentration of investigated solutes was not carried out because of the low dialysate concentration of protein [1.06 ± 0.36 (SD) g/liter after 360 min]. The concentration of electrolytes (sodium and potassium) in plasma water was corrected for the Donnan factor by multiplication with the correction factor 0.96 [20, 21]. The measured concentration of creatinine in the dialysate was corrected for the influence of glucose concentration in the dialysate [22, 23] according to the formula:

$$C_{creat} = C'_{creat} - 0.35 \cdot C_{glucose} \quad (2)$$

where C_{creat} is the corrected value of creatinine concentration; C'_{creat} is the measured value of creatinine concentration (both in μmol/liter); −0.35 is the correction factor obtained in our laboratory; and $C_{glucose}$ is the concentration of glucose in the dialysate at a given time (mmol/liter).

For the calculation of the peritoneal energy supply resulting from absorption of glucose the value 3.85 kcal/g of anhydrous dextrose absorbed was used [24].

For each of the three different glucose solutions the obtained values of K_{BD} for each solute were used to calculate the amount of solutes that would have been transported if diffusion had been the only transport mechanism (**Appendix**). [Note that the applied method for calculation of diffusive mass transport coefficient involves a simple mathematical model in which we by diffusion mean solute movement due to solute concentration difference with constant transport coefficient (K_{BD}), and in which the peritoneal membrane is regarded as a membrane with no active transport involved.] These data were compared with the total intraperitoneal amount (M_D) of solutes at each time (t) calculated using the formula:

$$M_{D(t)} = V_{D(t)} \cdot C_{D(t)} \quad (3)$$

where C_D is the concentration of the solute in the dialysate. The amount attributed to non-diffusive (that is, mainly convective) transport was obtained by subtraction of the diffusive component from the measured total amount of the solute. Note that the homogeneous membrane models for peritoneal transport imply that differences between overall and diffusive transport of small solutes can be attributed only to convective transport. However, the non-diffusive transport component may also include lymphatic absorption, and possibly other transport mechanisms. Thus, the current simplified approach to estimate non-diffusive transport does not enable us to delineate the details of peritoneal solute transport. On the other hand, the lymphatic absorption may account for only a minor portion of solute transport in peritoneal dialysis. Our previous calculations show that the impact of lymphatic flow on K_{BD} for small solutes (estimated during dialysate isovolemia) is ≤5% if lymphatic flow is 1 ml/min or less [14]. Furthermore, there is no evidence that transport mechanisms other than diffusion, convective transport and lymphatic absorption contribute substantially to peritoneal solute transport. Therefore, the presently applied approach can be considered to provide an approximate estimate of the relative importance of diffusive versus convective transport at different times of the dwell.

The initial intraperitoneal glucose amount (at time 0 min) was calculated as the sum of the amount of glucose in the bag prior to infusion and the intraperitoneal amount of glucose in the residual dialysate volume. The intraperitoneal amount of glucose in the residual dialysate volume was calculated as the product of the glucose concentration in the drained morning dialysate and the estimated intraperitoneal residual volume at 360 minutes. The calculated amount of glucose in the residual volume at time 0 minutes was on average 1.7 ± 1.1% of the total initial intraperitoneal amount of glucose.

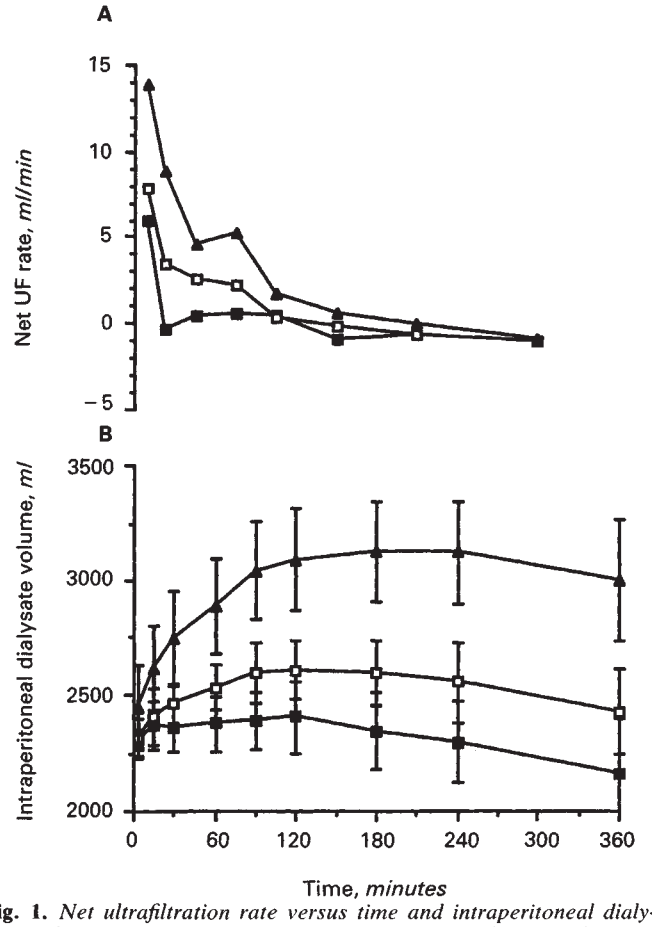

Fig. 1. *Net ultrafiltration rate versus time and intraperitoneal dialysate volume (mean ± SD) versus time during a six-hour single dwell study with an exchange of 2 liter of 1.36%* (N = 9, ■), *2.27%* (N = 9, □) *or 3.86%* (N = 23, ▲) *glucose solution.*

Statistical methods

Student's *t*-test for paired and unpaired data and calculation of the correlation coefficient were used to evaluate the results. When the three different glucose solutions were compared analysis of variance (ANOVA) was used for single and repeated measurements. When ANOVA single measurements showed significant differences Scheffe's F test was used to further analyze differences between groups. Data are expressed as mean ± SD, unless otherwise noted. Statistical significance was accepted if $P < 0.05$.

Results

Fluid transport

The intraperitoneal volume over time curves for the three different glucose concentrations are presented in Figure 1 showing that the maximum intraperitoneal volume (V_{Dmax}, Table 2) was higher and the time at which V_{Dmax} was obtained (T_{Vmax}) occurred later for solutions with a higher glucose concentration. As seen in Figure 1, net ultrafiltration occurred mainly during the first 15 minutes for the 1.36% dialysis fluid and during the first 90 minutes for both the 2.27% and the 3.86% dialysis fluid. The initial period of rapid net ultrafiltration (Fig. 1) was followed by a period of dialysate isovolemia (with volume changes of less than 2% per hr) lasting between 15 minutes and 120 minutes of the dwell for the 1.36% solution, between 90 and 240 minutes for the 2.27% solution, and between 120 and 240 minutes for the 3.86% solution. Finally, a period of net fluid reabsorption with a rate ($-\Delta V_D/\Delta t$, mean values: 1.0 − 1.1 ml/min; Table 2) independent of the initial glucose concentration in the dialysis fluid was observed in each of the 41 studies. As seen in Figure 1 the 2.27% glucose solution provided a volume over time curve which was closer to that of the 1.36% glucose solution curve than to that of the 3.86% glucose solution.

The K_E values were slightly higher for the 3.86% solution than for the other two solutions (Table 2), indicating faster elimination of RISA ($P < 0.01$, *t*-test between the 3.86% group, $N = 23$, and the combined material of the 1.36% and 2.27% group, $N = 18$). The fluid reabsorption rate between 240 and 360 minutes correlated both with K_E ($r = 0.532$, $P < 0.001$) and with the percentage of glucose absorbed at 360 minutes ($r = 0.385$, $P = 0.013$).

Glucose transport

The dialysate glucose concentration (Fig. 2) as well as the amount of glucose (Fig. 3) in the dialysate decreased exponentially with time in a uniform way. The percentage of the amount of glucose absorbed over time was almost identical for the three solutions (Fig. 3). The mean percentage of the initial amount of glucose which had been absorbed (%GA) at various times (t, min) during the dwell (from 3 to 360 min) could be described ($r = 0.999$) for all three solutions, using the experimental formula:

$$\%GA = 85 - 75.7 * e^{-0.005 * t} \quad (4)$$

At the termination of the dwell study, about 75% of the initial glucose amount had been absorbed for all three solutions (Fig. 3). Of the total amount of glucose absorbed about 50% was absorbed during the first 90 minutes of the dwell (Fig. 3). The corresponding peritoneal energy supply from glucose absorption for the three solutions is given in Table 3.

The energy load resulting from glucose absorption may represent a metabolic problem in CAPD patients [16, 17]. From a clinical point of view it may therefore be of value to achieve the most effective fluid removal relative to energy load. The ratio net ultrafiltration per kcal supplied from glucose absorption from the dialysate for the three different solutions was highest at the beginning of the dwell and higher for the more hypertonic solutions (Fig. 4). The net ultrafiltration per kcal ratio decreased linearly after 90 to 120 minutes for all three solutions. The ratio was 2.4 ± 3.6 ml/kcal, 3.9 ± 1.7 ml/kcal and 5.1 ± 2.8 ml/kcal at 120 minutes, and −1.7 ± 2.8 ml/kcal, 1.1 ± 1.4 ml/kcal and 2.6 ± 1.5 ml/kcal at 360 minutes for the 1.36%, 2.27% and 3.86% solution, respectively.

Blood glucose concentrations remained essentially stable with the 1.36% solution and showed only minor increases during the first hour for the 2.27% and 3.86% solution with the most pronounced increase for the 3.86% glucose solution [5.6 mmol/liter ($N = 23$) at 0 min vs. 7.6 ± 1.3 mmol/liter ($N = 17$, $P < 0.001$) at 60 min].

The diffusive mass transport coefficient (K_{BD}) for glucose did not differ between the three solutions (Table 4).

Table 2. Fluid transport characteristics

	N	V_D max ml	$T_{V\ max}$ min	V_{360} ml	V_{OUT} ml	V_{RES} ml	$-\Delta V_D/\Delta t$ ml/min	K_E ml/min
1.36%	9	2427 ± 127[c]	92 ± 39[b]	2157 ± 235[c]	1930 ± 224[c,d]	227 ± 117	1.1 ± 0.7	1.2 ± 0.3
2.27%	9	2642 ± 135[c]	160 ± 94	2429 ± 184[c]	2211 ± 179[c]	218 ± 110[a]	1.0 ± 0.7	1.2 ± 0.6
3.86%	23	3161 ± 231	197 ± 74	2997 ± 262	2612 ± 242	385 ± 194	1.0 ± 0.9	1.7 ± 0.6

Data are means ± SD. Abbreviations: V_D max, maximum intraperitoneal dialysate volume; T_{Vmax}, time to reach V_D max; V_{360}, intraperitoneal dialysate volume at 360 min; V_{OUT}, recorded dialysate effluent volume; V_{RES}, residual intraperitoneal volume at 360 min; $-\Delta V_D/\Delta t$, rate of net fluid reabsorption between 240 and 360 min; K_E, elimination rate of RISA from the peritoneal cavity.

Significant differences for the 1.36% group and the 2.27% group, respectively, vs. the 3.86% group are marked: [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$. Significant differences for the 1.36% group vs. the 2.27% group are marked: [d] $P < 0.05$

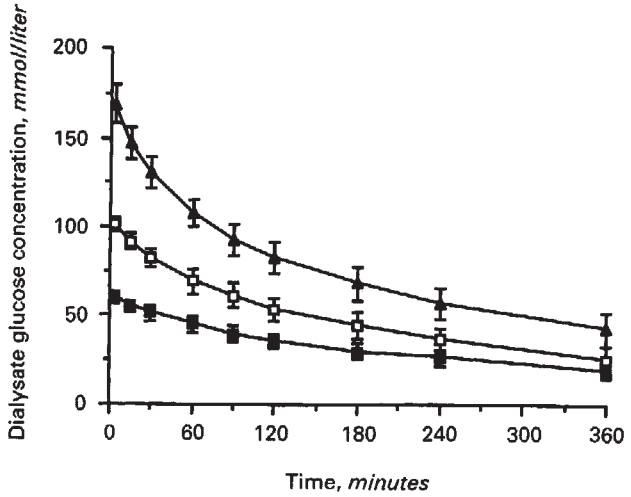

Fig. 2. *Intraperitoneal dialysate glucose concentration (mean ± SD) versus time during a six-hour single dwell study with 2 liter of 1.36%, 2.27% or 3.86% glucose solution.* Symbols as in Fig. 1.

Transport of other solutes

The K_{BD} values for urea, creatinine, potassium and total protein did not differ between the three solutions (Table 4). Note that K_{BD} for sodium was calculated only for the 3.86% glucose solution (Table 4) because for the 1.36% and 2.27% glucose solution the change in dialysate sodium concentration during dialysate isovolemia (Fig. 5) was too small to allow a reliable calculation of K_{BD} for sodium. The use of aqueous solute concentrations (**Methods**) in the calculations of K_{BD} yielded much lower values of K_{BD} for small solutes (with the exception of glucose) in comparison to K_{BD} values calculated using non-corrected plasma solute concentrations. In the current study the difference was found to be about 40% for urea, 20% for creatinine and 10% for potassium (data not shown).

There were small but statistically significant differences in K_{BD} values for total protein and creatinine between the patients with and the patients without previous peritonitis episodes, respectively. The K_{BD} values were: for total protein 0.116 ± 0.068 versus 0.069 ± 0.039 ml/min ($P < 0.05$), and for creatinine 11.6 ± 4.8 versus 8.5 ± 3.9 ml/min ($P < 0.05$) for the patients with ($N = 17$) and without ($N = 16$) previous peritonitis episodes respectively. However, there was no difference between the two groups as regards K_{BD} values for glucose, urea and potassium, nor as regards K_E, intraperitoneal dialysate volume curves, and fractional glucose absorption.

The dialysate sodium concentration decreased during the first 90 minutes with the most marked changes for the 3.86% solution whereas the dialysate potassium concentration did not differ between the three solutions (Fig. 5).

Plasma potassium, urea and creatinine concentrations remained essentially stable during the dwell study (data not shown) whereas the plasma sodium levels showed a slight increase when the 3.86% glucose solution was used (from 139.4 ± 2.7 mmol/liter at 0 min to 140.3 ± 2.4 mmol/liter at 360 min, $P < 0.01$, *t*-test). Plasma total protein decreased slightly during the dwell when the 1.36% and 2.27% solutions were used (from 67.8 ± 5.3 and 68.3 ± 6.6 g/liter at 0 min to 64.1 ± 4.9 and 64.3 ± 6.4 g/liter at 360 min, respectively, $P < 0.05$ and < 0.001, *t*-test) possibly due to positive fluid balance and dilution of the plasma concentration. During the use of the 3.86% solution, plasma total protein levels remained stable (65.4 ± 4.4 and 65.5 ± 5.5 g/liter at 0 and 360 min, respectively; NS).

The dialysate osmolality showed the same pattern as the dialysate glucose concentration (Fig. 6).

Calculated amounts transported by diffusion only

The methods for the assessment of the diffusive and non-diffusive components of solute transport are described in the **Appendix**. The total intraperitoneal amount of solutes over time in the dialysate was calculated for total protein (Fig. 7), glucose, creatinine, urea, potassium and sodium for each of the three solutions. The intraperitoneal amounts were compared with the calculated amounts, which according to equation A2 in the **Appendix**, may be assumed to have been transported by diffusion only (Figs. 8 and 9). The relative importance of non-diffusive transport vs diffusive transport was largest during the initial part of the dwell with the 3.86% glucose solution in which case non-diffusive transport after 60 minutes of dwell time accounted for about 30 to 40% of the total peritoneal transport of urea (29 ± 13%), creatinine (27 ± 16%) and potassium (40 ± 18%) (Fig. 8). The non-diffusive transport was less important for the 2.27% glucose solution and negligible for the 1.36% glucose solution (data not shown). Paradoxically the calculated net glucose disappearance rate from the peritoneal cavity was faster than the calculated rate due to diffusion only (Fig. 9); the calculated non-diffusive glucose transport was thus negative. This phenomenon was observed for all three glucose solutions.

Discussion

This is the first study which provides a detailed comparative analysis of peritoneal fluid and solute transport characteristics for the three most widely used glucose-based dialysis solutions

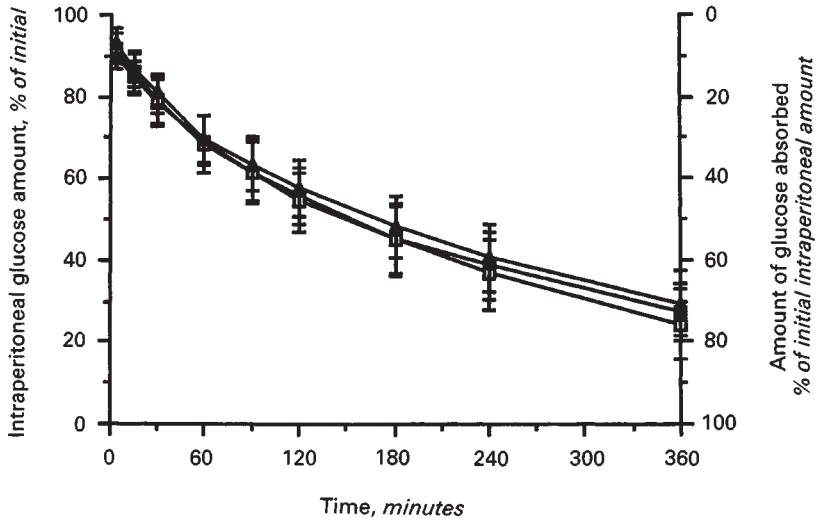

Fig. 3. *Intraperitoneal dialysate glucose (% of initial amount, mean ± SD) and percentage of glucose amount absorbed versus time during a six-hour single dwell study with 2 liters of 1.36%, 2.27% or 3.86% glucose solution.* Symbols as in Fig 1.

Table 3. Amount of glucose absorbed and corresponding peritoneal energy load at different times of the dwell (mean ± SD)

		Amount of glucose absorbed *g*						
	N	30 min	60 min	90 min	120 min	180 min	240 min	360 min
1.36%	9	6 ± 1	8 ± 1	11 ± 2	12 ± 2	15 ± 2	17 ± 2	20 ± 2
2.27%	9	10 ± 3	15 ± 4	18 ± 4	21 ± 4	25 ± 5	29 ± 5	35 ± 5
3.86%	23	15 ± 4	24 ± 5	29 ± 5	34 ± 6	41 ± 6	48 ± 7	56 ± 7
		Peritoneal energy load *kcal*[a]						
	N	30 min	60 min	90 min	120 min	180 min	240 min	360 min
1.36%	9	23 ± 5	33 ± 5	41 ± 7	47 ± 6	58 ± 7	65 ± 7	78 ± 6
2.27%	9	38 ± 11	56 ± 14	68 ± 14	81 ± 14	98 ± 17	113 ± 18	135 ± 19
3.86%	23	59 ± 14	93 ± 18	112 ± 21	130 ± 23	159 ± 25	183 ± 27	217 ± 26

[a] Energy of anhydrous dextrose: 3.85 kcal/g [24]

in CAPD patients. Special attention was paid to assure accurate intraperitoneal volume measurements as well as accurate determinations of solute transport parameters during a period of dialysate isovolemia, using aqueous solute concentrations. An attempt was made to quantitatively assess the relative importance of diffusive versus non-diffusive transport of small solutes. In the current study the intraperitoneal dialysate volume over time curve (Fig. 1) was characterized by the rate and duration of the initial positive net ultrafiltration (depending on the glucose osmotic pressure), the duration of dialysate isovolemia (long-lasting for the three solutions) and finally by the rate of fluid reabsorption (similar for all three solutions). The diffusive mass transport properties of the peritoneum did not seem to depend either on the initial dialysate concentration of glucose or on the ultrafiltration flow rate. The results of the present study indicate that although for small solutes diffusion is the dominating transport mechanism, non-diffusive (that is mainly convective) transport of small solutes contributes substantially to the overall peritoneal transport during the initial part of an exchange with hypertonic dialysis fluid; an alternative explanation could be that K_{BD} is variable and perhaps higher at the beginning of the dwell leading to overestimation of the non-diffusive transport component (vide infra).

Fluid transport

During the initial part of the dwell, net ultrafiltration (flow rate as well as duration) differed substantially between the three investigated dialysis solutions. The maximum initial (3 to 15 min) net ultrafiltration rate, which showed large interpatient variability, was found to be on the average 6 ml/min, 8 ml/min and 14 ml/min, respectively, with the three investigated solutions. Note the rapid fall of net ultrafiltration rate during the beginning of the dwell for all three solutions (Fig. 1). This change reflects the rapid dissipation of the osmotic driving force; however, other factors such as a change of the hydraulic conductivity of the peritoneal barrier can not be ruled out. In addition, incomplete mixing of the dialysate may result in a small but systematic underestimation of the volume at three minutes. The period of dialysate isovolemia was found to be long-lasting for all three solutions. The fluid reabsorption rate between 240 and 360 minutes was of the same magnitude, about 1 ml/min. During the entire period of fluid reabsorption there was still a positive glucose osmotic gradient. This gradient is counterbalanced by the colloid osmotic pressure, the hydrostatic pressure and the lymphatic flow [6, 25–29]. In fact, the model proposed by Rippe et al [27–29], which takes into

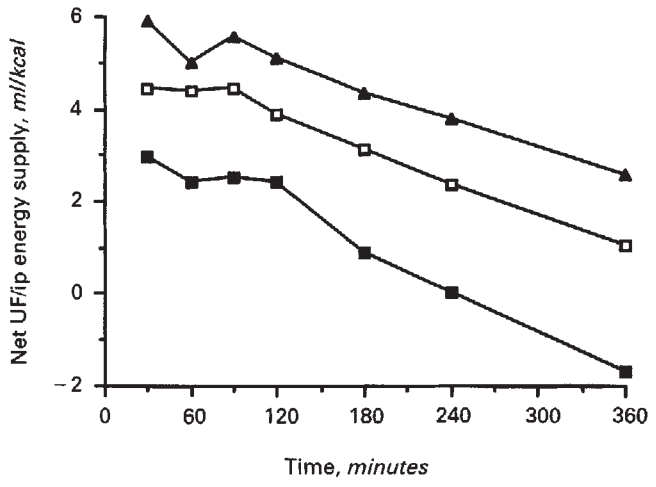

Fig. 4. *The mean ratio net ultrafiltration per energy supplied from glucose absorbed from the dialysate (Net UF/i.p. energy supply, ml/kcal) versus time during a six-hour single dwell study with 2 liters of 1.36%, 2.27% or 3.86% glucose solution.* Symbols as in Fig. 1.

account these phenomena, generates theoretical dialysate volume over time curves [29] which are in excellent agreement with the results of the current study.

The 2.27% glucose solution provided a volume over time curve which was surprisingly close to the volume curve of the 1.36% glucose solution. The present results suggest that a new medium strength glucose solution with a concentration of glucose between 2.27% and 3.86%, yielding an intermediary volume curve could be clinically more valuable than the current 2.27% glucose solution for the management of fluid balance in CAPD patients.

In most previous studies, the evaluation of volume over time profiles was either made without a tracer, or the disappearance rate of the tracer was not taken into account, leading to large errors in the determination of the dialysate volume at the end of the dwell [19, 30]. The volume over time profiles found in the current study are in agreement with previous studies in which dialysate volume assessments were based on measurements of the drained volume at different times of a single dwell [28] or on different dwell periods [31, 32] or using RISA [33], unlabelled albumin [34] or autologous hemoglobin [33, 35–37] as volume markers. However, there are only a few previous reports comparing intraperitoneal dialysate volume over time curves in CAPD patients using different glucose solutions [28, 31, 32]; none of these studies involved more than two different glucose concentrations.

In the current study the tracer disappearance rate (K_E) was assumed to be by first order kinetics, that is, K_E is constant and the amount of tracer eliminated from the peritoneal cavity is proportional to the dialysate concentration of the tracer. In some previous studies corrections for tracer elimination, assuming zero order kinetics was applied, that is, the amount of tracer removed per time unit was assumed to be constant and not influenced by the dialysate tracer concentration [36, 38]. This assumption is hard to defend from a theoretical point of view since it would suggest that the tracer elimination rate depends reciprocally on the tracer concentration in the dialysate. However, the application of zero versus first order kinetics of tracer elimination results in almost identical dialysate volume over time curves.

The elimination rate of RISA (K_E), which is an estimate of albumin transport from the peritoneal cavity into the lymphatics and into adjacent tissues, was found to be similar to previously reported values of tracer elimination rate using unlabelled albumin [34], RISA [39], dextran [40] and autologous hemoglobin [36, 37, 39] as volume markers. In the current study K_E was slightly higher for the 3.86% solution than for the two weaker solutions. Lymphatic absorption is known to be influenced by hydrostatic pressure [25, 41] and it is possible that the larger dialysate volume, and thus increased hydrostatic pressure [42] during peritoneal dialysis with the 3.86% solution may increase the lymphatic absorption of fluid (and perhaps also increase losses of RISA into adjacent tissues). The hypothesis that the hydrostatic pressure can have an impact on the rate of lymphatic absorption is also in line with the previous observation that the tracer elimination rate is higher during a three liter exchange compared to a two liter exchange with 1.36% glucose solution [36]. Volume calculations using first order kinetics with constant tracer elimination coefficient could therefore result in a slight error in the determination of dialysate volume.

In the current study, K_E and the fluid reabsorption rate were of the same order of magnitude, 1 to 2 ml/min (Table 2), and there was a positive correlation between these two variables. This may suggest that K_E and the fluid reabsorption rate reflect lymphatic absorption [43]. However, the magnitude of the lymphatic flow rate in CAPD patients is controversial [44–47] since the appearance rate of the tracer in blood is only 10 to 20% of the disappearance rate from the peritoneal cavity [40, 48–51].

Diffusive solute transport

For the calculation of the diffusive mass transport coefficient (K_{BD}) plasma small solute concentrations were expressed as aqueous solute concentrations, that is corrected for plasma protein concentration, and for electrolytes also with a correction applied for the Donnan factor. This correction resulted in K_{BD} values which were substantially smaller than K_{BD} values obtained using plasma solute concentrations for all the investigated small solutes except glucose. The difference was especially large for urea, for which K_{BD} was on average about 40% lower compared to uncorrected values. These results show the importance of using aqueous instead of plasma solute concentrations for K_{BD} calculations for substances which equilibrate rapidly [20].

The diffusive mass transport parameter (K_{BD}) for small solutes did not differ between the three solutions, indicating that the diffusive transport properties of the peritoneal membrane were not influenced by the three solutions. Thus, no impact of different volumes or glucose concentrations within the investigated range could be demonstrated. However, a small difference in K_{BD} values between the different glucose solutions cannot be excluded since the same patients were not studied with the three different solutions. It is also possible that volume differences at the time of dialysate isovolemia were too small to demonstrate a possible influence of dialysate volume on (isovolumetric) K_{BD}. In the previous study by Spencer and Farrell [40] concerning the possible influence of dialysate volume and glucose concentration on K_{BD} values for urea and

Table 4. Diffusive mass transport coefficients (K_{BD}) for investigated substances (mean ± SD)

		K_{BD} *ml/min*					
	N	Glucose	Urea	Creatinine	Sodium	Potassium	Total protein
1.36%	9	9.6 ± 3.7	18.1 ± 3.5	12.4 ± 3.9	NC	13.6 ± 4.3	0.10 ± 0.03
2.27%	9	10.7 ± 2.7	17.0 ± 4.0	10.2 ± 4.5	NC	14.8 ± 6.6	0.11 ± 0.09
3.86%	23	10.6 ± 2.5	17.1 ± 3.2	9.3 ± 4.2	4.6 ± 2.6	10.4 ± 4.6	0.08 ± 0.04

NC = Not calculated because the change in dialysate sodium concentration during dialysate isovolemia (Fig. 6) was too small to allow a reliable calculation of K_{BD} for sodium.

Statistical analysis (ANOVA) showed no statistically signifiant difference in K_{BD} values for the investigated substances between the three different glucose dialysis solutions.

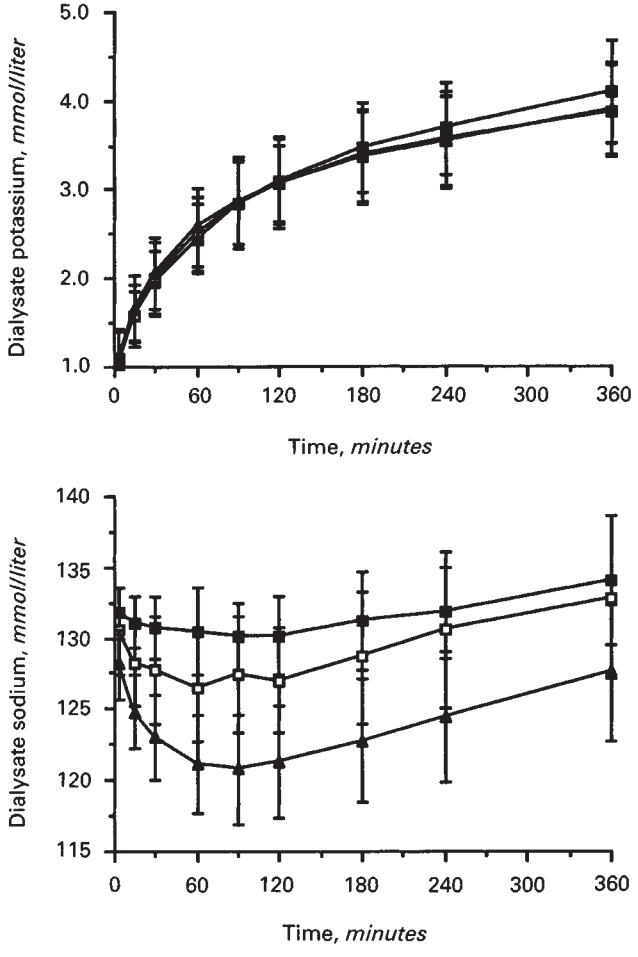

Fig. 5. *Dialysate potassium and sodium concentration (mean ± SD) versus time during a six-hour single dwell study with 2 liters of 1.36%, 2.27% or 3.86% glucose solution.* Symbols as in Fig. 1.

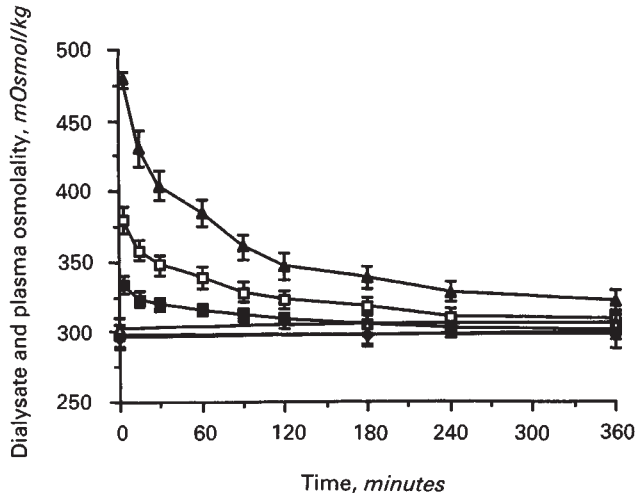

Fig. 6. *Dialysate and plasma osmolality (mean ± SD) versus time during a six-hour single dwell study with 2 liters of 1.36%, 2.27% or 3.86% glucose solution.* Dialysate symbols as in Fig. 1. Plasma symbols are: 1.36% (N = 9, ◆), 2.27% (N = 9, ◇) and 3.86% (N = 23, △).

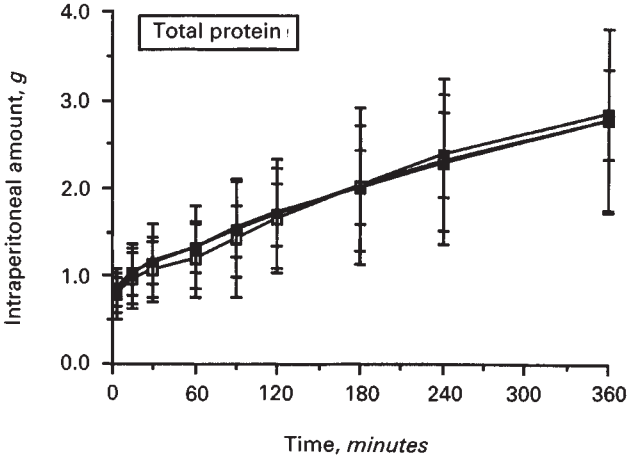

Fig. 7. *The measured intraperitoneal amount of total protein (mean ± SD) versus time during a six-hour single dwell study with 2 liters of 1.36%, 2.27% or 3.86% glucose solution.* Symbols as in Fig. 1.

creatinine, a higher K_{BD} for urea but not for creatinine was found in twelve CAPD patients studied with a two liter exchange of 1.36% glucose solution compared to a one liter exchange. In a study comparing two and three liter exchanges with 1.36% glucose solutions, Krediet et al [36] found significantly higher peritoneal mass transfer area coefficients for creatinine, kanamycin and inulin using the larger volume but no difference for urea, lactate, glucose, β_2-microglobulin, albumin or IgG. Furthermore, no difference in K_{BD} for urea and creatinine between 1.36% and 3.86% glucose solutions was found in five CAPD patients investigated [40]. The use of a 7% glucose solution for peritoneal dialysis in uremic patients has been associated with an increased solute clearance which exceeded the possible contribution of convective transport [52] and this effect was still observed in lesser degree during a

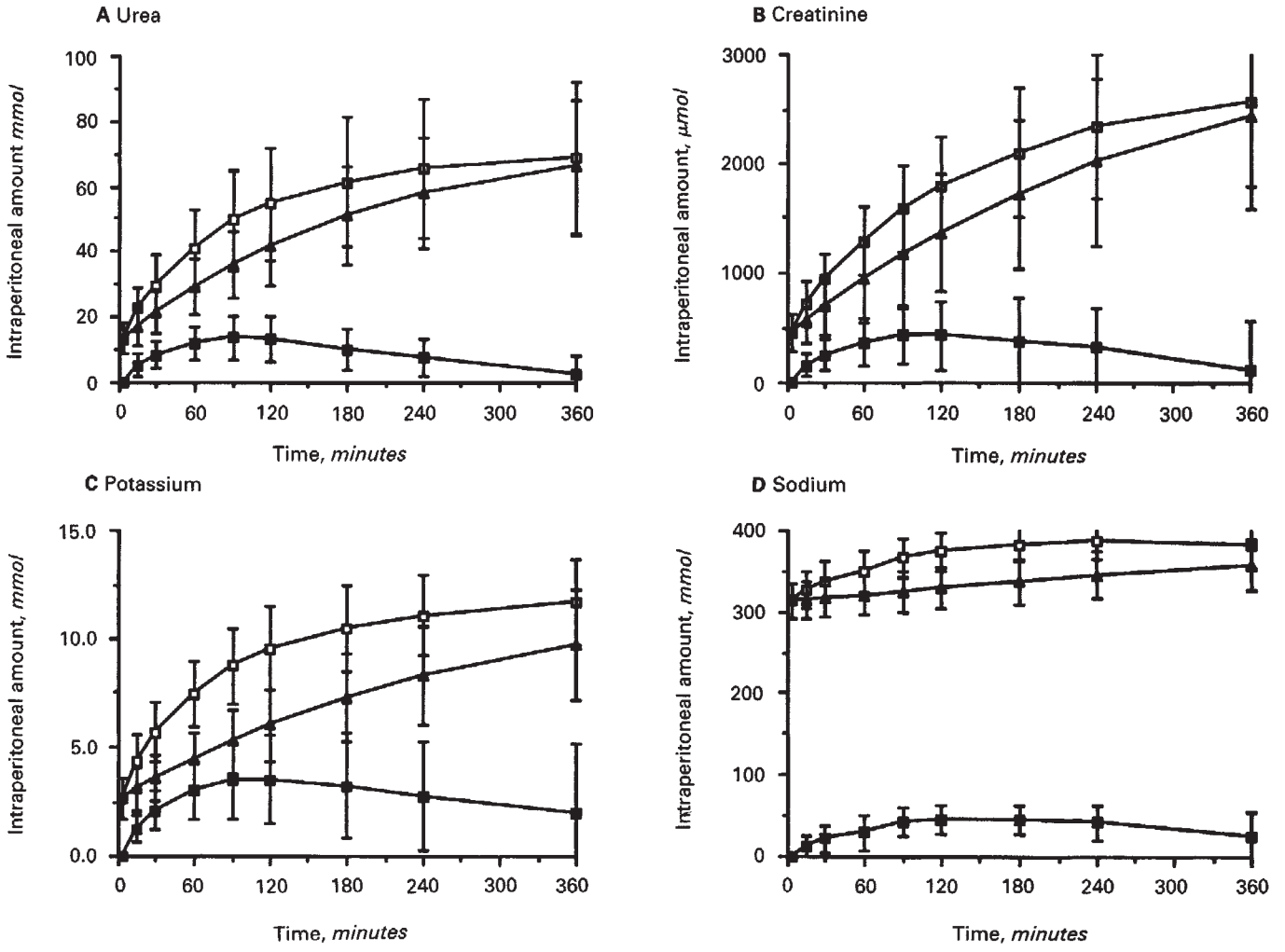

Fig. 8. *The measured total intraperitoneal amount (□), the calculated amount that would have been transported if diffusion had been the only transport mechanism (▲) and the calculated amount transported due to non-diffusive transport (■) for urea, creatinine, sodium and potassium in patients studied with 3.86% glucose solution (mean ± SD, N = 23).*

subsequent exchange of isotonic dialysis fluid [52, 53]. However, such an effect was not seen in rabbits studied with 4.25% and 1.25% glucose solution [54].

The observed decrease of dialysate sodium during the initial period of rapid ultrafiltration (Fig. 5), indicates sodium sieving through the peritoneal barrier [12, 13, 20]. The finding that dialysate sodium concentration decreases substantially with the hypertonic 3.86% glucose solution and that plasma sodium concentration increases slightly, indicate that very short dwell times with hypertonic glucose solution may lead to low sodium removal relative to fluid removal. This may result in hypernatremia [55], especially in patients treated with rapid exchanges of hypertonic glucose solution with a cycler. To avoid this dialysis fluid with lower sodium concentration may be of value.

Non-diffusive solute transport

The estimated non-diffusive transport (which mainly should consist of convective transport) contributes substantially to the overall transport of creatinine, urea, potassium and sodium during the initial period of the exchange with 3.86% glucose solution (Fig. 8). Thus, the convective transport plays an important role in enhancing net peritoneal clearance for these solutes when hypertonic solutions and short dwell periods are used [7]. Note that the postulated existence of a peritoneal tissue compartment (vide infra) could result in variable K_{BD} values during the dwell. Therefore, the application of models in which K_{BD} is assumed to be constant may not be appropriate for the correct estimation of non-diffusive transport.

Although K_{BD} for total protein was calculated during a period of dialysate isovolemia, the phenomenological parameter K_{BD} does not exclude the possibility that convective transport is the dominating feature of transperitoneal macromolecular transport. There is strong evidence that transcapillary exchange of macromolecules is mainly by convective transport through large pores [56–58]. Therefore an estimation of the relative importance of diffusive versus non-diffusive transport was not carried out for total protein in the current study. However, the finding that the intraperitoneal amount of total protein was almost identical over time with the three different glucose solutions (Fig. 7) indicates that transport of total protein

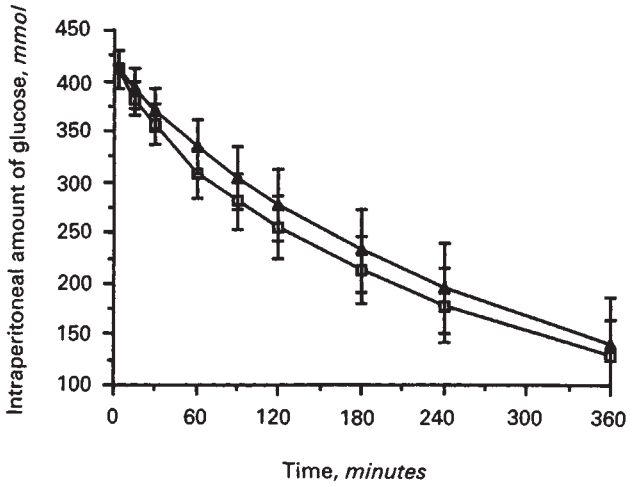

Fig. 9. *The measured total intraperitoneal amount of glucose (□) and the calculated amount of glucose in the peritoneal cavity when glucose transport was calculated to be by diffusion only (▲) in patients studied with 3.86% glucose solution (mean ± SD, N = 23).* Note that glucose disappears faster from the peritoneal cavity than expected from diffusion only.

through the peritoneal barrier is not influenced by the differences in glucose concentration or ultrafiltration rate.

Glucose transport

The fractional glucose absorption, expressed as a percentage of the initial intraperitoneal amount of glucose, was almost identical for all three solutions (Fig. 3), and similar to previous observations in patients using different dwell times and different glucose solutions [5, 59, 60]. The absorbed amount of glucose provides a substantial energy supply (Table 3). Thus, a patient using four 1.36% two liter bags will absorb about 80 g glucose/24 hr corresponding to 300 kcal/24 hr and a patient using four 3.86% two liter bags will absorb about 220 g glucose/24 hr corresponding to 850 kcal/24 hr. This is in keeping with the reported average daily absorption of 100 to 200 g glucose in CAPD patients [61–65]. Patients with decreased ultrafiltration capacity need more frequent exchanges with hypertonic solutions. In addition, the glucose absorption rate is often increased in these patients [14], resulting in an even larger peritoneal caloric load.

The relationship between net ultrafiltration and the peritoneal energy load from glucose absorption (Fig. 4) shows that the net fluid removal per kcal supplied from glucose absorption was highest with the 3.86% glucose solution compared to the less hypertonic solutions (Fig. 4). Thus, to achieve the most effective fluid removal relative to glucose absorption, hypertonic glucose solutions with short dwell times should be used; however, this may result in hypernatremia (vide supra) as well as in hyperglycemia [1, 17].

The observation that the fractional absorption of glucose was almost identical for the three solutions, indicates that the peritoneal transport of glucose is mainly by diffusion and thus that convective transport of glucose plays only a minor role. Note that during positive ultrafiltration the fluid flow is from blood to dialysate which is in the opposite direction than the net diffusive transport of glucose from dialysate to blood. Since the concentration of glucose in the ultrafiltered fluid (osmotically driven from blood) is much smaller than in the dialysate, this fluid flux should diminish the rate of glucose diffusion from the peritoneal cavity to blood. In contrast, the calculated net glucose disappearance rate from the peritoneal cavity was faster than the estimated rate due to diffusion only (Fig. 9) and the calculated non-diffusive glucose transport was thus negative for all three glucose solutions. This paradoxical observation is in agreement with our previous theoretical evaluation using the Pyle-Popovich model [12, 20]. When using glucose as osmotic agent the sieving coefficient for glucose (calculated using the Pyle-Popovich model) was found to be negative (that is, out of the physically interpretable range), indicating that glucose is transported faster from the peritoneal cavity than expected from the K_{BD} values obtained with the model [12, 20]. Thus, the results of the current study as well as the previous application of the Pyle-Popovich model [12, 20] shows that, although peritoneal transport models in which the peritoneal barrier is regarded as a homogeneous membrane can give a proper description of peritoneal solute transport for clinical purpose [12], they cannot provide a theoretically correct description of glucose transport at least when glucose is used as osmotic agent in the dialysis fluid. Similarly, in the application of the three-pore model in which theoretical and literature data were used to fit experimental data to the calculated volume over time curve for different glucose solutions, Rippe, Stelin and Haraldsson [29] had to introduce inflated K_{BD} values for glucose in order to obtain a reasonably good fit of simulated to experimental data. In the study by Rippe et al, the assumed K_{BD} value for glucose was increased by about 50%, to 15.5 ml/min, from the theoretically predicted value of 10.2 ml/min [29]. Note that the K_{BD} value for glucose predicted by Rippe et al [29], 10.2 ml/min, is similar to the value found in the current study (Table 4) and in agreement also with previously reported data for clinically stable CAPD patients [6, 38, 66–68].

The puzzling observation in the current study that glucose disappearance from the peritoneal cavity was faster than expected (from the calculated rate of diffusion of glucose), especially during the initial part of the dwell (Fig. 9), may perhaps be related to the postulated existence of a peritoneal tissue compartment in which the concentrations of solutes are equilibrating (with some time lag) with the dialysate compartment [19, 69]. This process may result in higher K_{BD} values during the beginning of the dwell [29, 70]. Furthermore, active transport of glucose into cells (where it is metabolized) is not taken into account in currently used peritoneal transport models. Due to rapid glucose absorption, the average blood glucose concentration in the capillaries surrounding the peritoneal cavity is probably higher than the concentration in systemic blood used for the calculation of K_{BD} for glucose. Such a discrepancy would lead to an underestimation of the diffusive mass transport coefficient (K_{BD}) for glucose. However, the problem of apparent negative non-diffusive glucose transport remains unsolved.

Summary and conclusions

During a six-hour peritoneal dialysis dwell with standard glucose-based dialysis fluids, the rate and duration of initial positive net ultrafiltration was proportional to the dialysate glucose concentration (Table 2, Fig. 1). The fluid reabsorption rate, however, did not differ between the three investigated

solutions (Table 2, Fig. 1), indicating that it was not influenced by the dialysate glucose concentration and that the combined effect of the three major determinants of the peritoneal fluid reabsorption rate (the colloid osmotic pressure, the hydrostatic pressure and the lymphatic flow rate) was constant. The hypertonic dialysis fluids provide a substantial peritoneal energy supply from absorption of glucose from the dialysate (Table 3, Figs. 2 and 3). On the other hand, to achieve maximum net ultrafiltration relative to glucose absorption (Fig. 4), hypertonic solutions with short dwell times should be used. This may result in hyperglycemia, as well as in hypernatremia due to the more rapid fluid relative to sodium transport rate through the peritoneal barrier (Fig. 5), but during a six hour dwell the effect of hypertonic solutions on plasma osmolality is negligible (Fig. 6).

The K_{BD} values for urea, creatinine, glucose, potassium and total protein did not differ between the three different solutions (Table 4), and the fractional absorption of glucose was almost identical (Fig. 3), indicating that the diffusive transport properties of the peritoneum does not depend on the dialysate concentration of glucose or on the ultrafiltration flow rate. The intraperitoneal appearance rate of total protein was almost constant and did not differ between the three solutions (Fig. 7). The calculated non-diffusive (that is, mainly convective) transport of small solutes (other than glucose) was found to be substantial during the initial part of an exchange with hypertonic solution and accounted for about 30 to 40% of the total transport of urea, creatinine and potassium during the first 60 minutes of the 3.86% exchange (Fig. 8). Paradoxically the calculated non-diffusive transport for glucose was found to be negative (Fig. 9), indicating that glucose is transported faster from the peritoneal cavity than would be expected from diffusion only. This suggests that peritoneal transport models based on passive transport through the homogeneous membrane with constant diffusive mass transport coefficient (K_{BD}) cannot provide a theoretically correct description of glucose transport at least when glucose is used as osmotic agent in the dialysis fluid. Thus, the applied methods have helped us to identify an inherent problem in the clinically used models based on these assumptions [2, 3, 6, 8–14, 35–38, 40, 52, 66–68].

Acknowledgments

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Appendix

Assessment of diffusive and non-diffusive components of solute transport in peritoneal dialysis

The total amount of a solute, M_D, in the dialysate is a product of the solute concentration, C_D, and the dialysate volume, V_D, that is, $M_D = C_D V_D$. The rate of change of M_D, dM_D/dt, is equal to the net flow of solute between blood and dialysate. This flow consists of three components: 1) *diffusive flow* which is proportional to differences between concentrations of the solute in blood, C_B, and dialysate, C_D, with K_{BD} as the coefficient of proportionality; 2) *convective flow* which is dependent on ultrafiltration rate, concentration of the solute in the membrane and sieving coefficient; and 3) *lymphatic uptake* which is dependent on the lymphatic flow rate and C_D [6, 12]. The lymphatic uptake accounts for a relatively minor fraction of the total peritoneal transport of solutes [12, 14] and this transport route is neglected in the following calculations.

To assess the relative importance of the diffusive and convective components in peritoneal mass transport a stepwise procedure was applied in which we first considered the diffusive transport only. A hypothetical situation was assumed that solutes are transported by diffusion only in spite of the water flow between blood and dialysate resulting in convective transport of solutes. Thus we applied the following equation:

$$dM_D/dt = K_{BD}(C_B - C_D) \quad \text{(A1)}$$

where $C_D = M_D/V_D$. Analytical solution of equation (A1) for constant C_B and V_D can be expressed as follows:

$$M_D(t_2) = C_B V_D + (M_D(t_1) - C_B V_D)\exp \quad \text{(A2)}$$

$$(-K_{BD}(t_2 - t_1)/V_D)$$

for time interval from t_1 to t_2. The assumption of relatively constant blood concentrations of the investigated solutes was fulfilled in this study for the whole dwell time, whereas dialysate volume changed significantly especially in dwell studies with hypertonic solution. Therefore we applied equation (A2) for each time interval between two consecutive measurements at 3, 15, 30, 60, 90, 120, 180, 240, and 360 minutes, respectively, taking V_D equal to the arithmetic average of the dialysate volume for the particular interval. The maximum change of V_D during these time intervals was lower (on average 6.8% for the 3.86% glucose solution between t_1 = 3 min and t_2 = 15 min) than the change of V_D during whole dwell study (on average 21.9%, Fig. 1).

The value of M_D calculated from equation (A2) for K_{BD} estimated during dialysate isovolemia was assumed to represent the fraction of solute amount in dialysate that would be a result of diffusive transport. The amount of the solute that can be attributed to non-diffusive (convective) transport was then obtained by subtracting the diffusive component [equation (A2)] from the experimentally-found total amount of the particular solute.

The justification for this approach to assess non-diffusive transport is that the mathematical models for peritoneal transport in which simultaneous diffusive and convective transport parameters are estimated, may yield unphysiological values of the convective transport coefficient of proportionality; thus the sieving coefficient for some substances have been found to be negative or exceed one [12].

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