LUND UNIVERSITY

Mass transfer of calcium across the peritoneum at three different peritoneal dialysis fluid Ca2+ and glucose concentrations.

Simonsen, Ole; Venturoli, Daniele; Wieslander, Anders; Carlsson, Ola; Rippe, Bengt

Published in:
Kidney International

DOI:
10.1046/j.1523-1755.2003.00055.x

2003

Link to publication

Citation for published version (APA):
Simonsen, O., Venturoli, D., Wieslander, A., Carlsson, O., & Rippe, B. (2003). Mass transfer of calcium across the peritoneum at three different peritoneal dialysis fluid Ca2+ and glucose concentrations. *Kidney International*, *64*(1), 208-215. https://doi.org/10.1046/j.1523-1755.2003.00055.x

Total number of authors:
5

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Kidney International, Vol. 64 (2003), pp. 208–215

Mass transfer of calcium across the peritoneum at three different peritoneal dialysis fluid Ca^{2+} and glucose concentrations

Ole Simonsen, Daniele Venturoli, Anders Wieslander, Ola Carlsson, and Bengt Rippe

Department of Nephrology, University Hospital of Lund, Lund, Sweden; and Corporate Research, Gambro AB, Lund, Sweden

Mass transfer of calcium across the peritoneum at three different peritoneal dialysis fluid Ca^{2+} and glucose concentrations.

Background. In peritoneal dialysis, the rate of ultrafiltration has been predicted to be a major determinant of peritoneal calcium (Ca^{2+}) removal. Hence, dialysis fluid glucose concentration should be an important factor governing the transperitoneal Ca^{2+} balance. The aim of this study was to test the effect of various dialysate glucose levels and selected dialysate Ca^{2+} levels on Ca^{2+} removal in peritoneal dialysis patients.

Methods. Patients ($N = 8$) received, during a 7-week period, 2 L of lactate (30 mmol/L)/bicarbonate (10 mmol/L)–buffered peritoneal dialysis solutions containing either 1.5% glucose and 1.0 mmol/L Ca^{2+} or 2.5% glucose and 1.6 mmol/L Ca^{2+}, or 4% glucose and 2.5 mmol/L Ca^{2+}, respectively, provided in a three-compartment bag (trio system). Patients underwent standardized (4-hour) dwells, one for each of the three dialysates to assess permeability-surface area product (PS) or mass transfer area coefficients (MTAC) for ionized and "freely diffusible" Ca^{2+}, lactate, glucose, bicarbonate, phosphate, creatinine, and urea.

Results. There was a clear-cut dependence of peritoneal Ca^{2+} removal on the rate of ultrafiltration. For large peritoneal to dialysate Ca^{2+} gradients (2.5 mmol/L Ca^{2+} in 4% glucose) a close fit of measured to simulated data was predicted by the three-pore model using nonelectrolyte equations. For low transperitoneal Ca^{2+} concentration gradients, however, directly measured Ca^{2+} data agreed with the simulated ones only when the peritoneal Ca^{2+} PS was set lower than predicted from pore theory (6 mL/min).

Conclusion. There was a marked ultrafiltration dependence of transperitoneal Ca^{2+} transport. Nonelectrolyte equations could be used to simulate peritoneal ion (Ca^{2+}) transport provided that the transperitoneal ion concentration gradients were large. Based on our data 1.38 mmol/L Ca^{2+} in the dialysis fluid would have created zero net Ca^{2+} gain during a 4-hour dwell for 1.5% glucose, whereas 1.7 and 2.2 mmol/L Ca^{2+} would have been needed to produce zero Ca^{2+} gain for 2.5% glucose and 3.9% glucose, respectively.

Key words: peritoneal dialysis, capillary permeability, ion transport, solute transport, macromolecules, computer simulation.

Received for publication February 4, 2002
and in revised form September 25, 2002, and December 12, 2002
Accepted for publication February 24, 2003

© 2003 by the International Society of Nephrology

In conventional solutions used for peritoneal dialysis, dialysis fluid sodium (Na^+) and calcium (Ca^{2+}) concentrations are adjusted to be rather close to their equilibrium plasma concentrations. This reduces their potential for diffusive transport, and hence, the exchange of these ions is highly dependent of their convective transport by "ultrafiltration" (i.e., by glucose-induced osmosis). Indeed, a number of previous studies have suggested that peritoneal Ca^{2+} removal in continuous ambulatory peritoneal dialysis (CAPD) be positively correlated to the degree of ultrafiltration [1–7]. For example, in the studies of peritoneal Ca^{2+} balance by Kwong, Lee, and Chan [1], Delmez et al [2], and Weinreich et al [3], hypertonic glucose exchanges (3.86%), resulted in Ca^{2+} net loss, even though dialysate Ca^{2+} was as high as 1.75 mmol/L, which would have favored peritoneal-to-plasma Ca^{2+} diffusion. This indicates that, when 3.86% glucose is employed as a peritoneal dialysis fluid, net Ca^{2+} transport occurs *against* the diffusive gradient (i.e., from plasma to peritoneum). Thus, the convective flux of Ca^{2+} is opposite to, and "overwhelming," the diffusive gradient at high rates of ultrafiltration (i.e., at high dialysate glucose concentrations).

In a previous study, Rippe and Levin [8] computer-simulated Ca^{2+} transport, or actually Ca^{2+} gain, over dwell time during CAPD as a function of dialysis fluid glucose concentration, and hence, the rate of ultrafiltration, and dialysis fluid Ca^{2+} concentration, using the three-pore model of peritoneal transport [9–11]. This computer simulation study confirmed and extended previous observations of a marked ultrafiltration dependence of Ca^{2+} transport and also that convective transport *against* the diffusion gradient can be the dominating transport mode when dialysate glucose concentration is high [1–3, 6, 7]. Actually, it was shown that a completely "neutral" Ca^{2+} balance across the peritoneal membrane during a 4-hour glucose dwell (i.e., a situation where ionized or diffusible Ca^{2+} is neither gained nor lost during 4 hours) was obtained for a dialysis fluid Ca^{2+} concentration of 1.35, 1.7,

Table 1. Composition of the peritoneal dialysis solutions investigated

Glucose concentration	1.5%	2.5%	3.9%
$MgCl_2$	0.25 mmol/L	0.40 mmol/L	0.62 mmol/L
$CaCl_2$	1.0 mmol/L	1.6 mmol/L	2.5 mmol/L
NaCl	132 mmol/L	132 mmol/L	132 mmol/L
Bicarbonate	10.2 mmol/L	10.0 mmol/L	9.7 mmol/L
Lactate	30.6 mmol/L	30.0 mmol/L	29.2 mmol/L

and 2.3 mmol/L for 1.36%, 2.27%, and 3.86% glucose in the peritoneal solution, respectively [8].

The major aim of the present study was, based on experimental data, to test the predictability of our previous computer simulations regarding Ca^{2+} gain for three different glucose concentrations in CAPD patients and, for the first time, to calculate an apparent Ca^{2+} permeability surface area product (PS), or mass transfer area coefficient (MTAC) using nonelectrolyte equations. Especially, we wanted to test solutions with Ca^{2+} concentrations as close as possible to the ones we had predicted to create a completely "neutral" peritoneal Ca^{2+} balance during a 4-hour dwell for an average patient with plasma ionized Ca^{2+} at 1.25 mmol/L. For manufacturing and logistic reasons, however, due to the fact that we tested a three-compartment system (trio system), with a certain stoichiometry between Ca^{2+} and glucose in the two small compartments containing the concentrated glucose, the latter goal was fulfilled only for one of the three glucose concentrations. We chose the 2.5% glucose solution to be Ca^{2+} neutral. For logistic reasons, the 1.5% glucose solution had to contain less Ca^{2+} than predicted for a Ca^{2+}-neutral solution, whereas the 3.9% glucose contained a higher dialysis fluid Ca^{2+} concentration (2.5 mmol/L) than had been predicted previously. It could thus be anticipated that only the 2.5% glucose solution would be completely Ca^{2+} neutral, while there would be a net Ca^{2+} loss for the 1.5% and a net Ca^{2+} gain for the 2.5% glucose solution, respectively.

METHODS

This study was an open, prospective study including one treatment group originally containing 10 patients with terminal renal failure and on CAPD for at least 3 months prior to the start of the study. The patients were allocated to use a new three-compartment system (trio system), containing three different Ca^{2+} concentrations, one for each glucose concentration, and largely devoid of glucose degradation products (GDP) [12], and furthermore, with 10 mmol/L/30 mmol/L bicarbonate/lactate as a buffer. The treatment period was 7 weeks. The composition of the new solution(s) with respect to concentrations of glucose, Ca^{2+}, and buffer/electrolytes is shown in Table 1.

During the 7 weeks of treatment using the new solution, each patient underwent, in a randomized fashion, three standardized dwell studies (4 hours), one for each solution, namely at week 1, at week 4, and at week 7 after inclusion. Between the dwell studies, at least 2 weeks had to elapse, during which CAPD was carried out according to our general routines and the patients' individual needs with respect to choice of glucose concentration in the bag using the trio system. A conventional 1.5% glucose solution containing 1.25 mmol/L Ca^{2+} was normally used as the overnight dwell preceding each test dwell.

The patients gave written informed consent, and the study was approved by the Regional Ethics Committee at Lund University.

Standardized dwell studies

^{125}I-albumin (RISA; Human Serum Albumin, Kjeller, Norway) was used as a volume marker in the standardized dwell studies by adding 0.185 mBq RISA to the solution (after mixing the appropriate compartments to obtain the desired glucose concentration) by aseptic techniques together with 2 g/L of "cold" human serum albumin (Immuno, Vienna, Austria) to prevent undue binding of RISA to bags and tubings. The level of free iodine was less than 1.5%. The patients were given 1 mmol of KCl on the night before the test dwells, in order to prevent any uptake of free (unlabeled) iodine by the thyroid.

The patients were investigated in the sitting position. After instillation of the test solution containing RISA, dialysate samples (5 mL/sample) were collected at 0, 5, 10, 20, 60, 90, 120, and 240 minutes, while blood samples (2 mL/sample) were taken at 0, 20, 60, 90, 120, 180, and 240 minutes. The frequent blood sampling was done mainly in order to be able to calculate the RISA clearance to plasma (Cl → P). Blood and dialysate samples were taken for total Ca^{2+} and ionized Ca^{2+}, lactate, glucose, urea, creatinine, sodium, phosphate, magnesium (Mg^{2+}), bicarbonate, and RISA. Dialysate sampling was performed by puncture of the injection port after draining approximately 400 mL of the dialysate into the empty bag. The solution was immediately reinstilled intraperitoneally after each sampling. The cumulative dialysate volume sampled represented only 1% to 2% of total intraperitoneal volume.

Bicarbonate samples were kept on ice and transported immediately to the laboratory. Bicarbonate was assessed as "standard bicarbonate." The rest of the samples, taken in heparin tubes, were collected and transported and analyzed at the end of each dwell session. All samples were analyzed according to current hospital routines using a Beckman Syncron LX 20 Autoanalyzer (Beckman Coulter, Fullerton, CA, USA). Creatinine was analyzed using the Jaffé method and values were corrected for the influence of glucose. Urea was determined using the

glutamate technique, glucose by the hexokinase method, phosphate using the molybdate technique, lactate using the lactate oxidase technique, serum albumin using cresol bromide purple, and ionized Ca^{2+} was measured using an ion-selective electrode (Radiometer ABL 505, Copenhagen, Denmark). Total calcium was assessed using the Beckman Syncron LX20-1 Master Instrument (i.e., not by flame photometry). The technique for sodium measurements in dialysis fluid had, according to our Central Laboratory routines, not been validated and certified, and was therefore not considered reliable. Therefore, no sodium data are presented in this paper. Due to difficulties in differentiating freely diffusible (and ionized) Mg^{2+} from total Mg^{2+}, especially for PS measurements, any magnesium measurements are not presented in this paper.

Calculations

PS (MTAC), as defined in previous publications [9–11], was calculated by a curve-fitting procedure (least squares) by adapting the outcome of the three-pore model to the experimental data in order to minimize the function

$$SSQ = \sum_t [C_{exp}(t) - C_{3p}(t)]^2 \qquad \text{(Eq. 1)}$$

where $C_{exp}(t)$ and $C_{3p}(t)$ are the dialysate solute concentration measured and calculated by the three-pore model, respectively, and the sum is extended to the whole dwell time. The minimization procedure was repeated for each of the solutes considered in the study.

Nonprotein-bound Ca^{2+} exists in the form of ionized Ca^{2+} and also as "freely diffusible" Ca^{2+}(i.e., the sum of ionized Ca^{2+} and Ca^{2+} complexed to lactate, bicarbonate, or phosphate). The concentration of freely diffusible Ca^{2+} in plasma (C_{FP}) was calculated according to [13]:

$$C_{FP} = C_{IP} + 0.01 \cdot AG + 0.0091 \cdot BIC \qquad \text{(Eq. 2)}$$

where C_{IP} is the plasma ionized Ca^{2+}, AG is the anion gap (15 mmol/L) while BIC symbolizes "standard bicarbonate." C_{FD} in dialysate was assessed from [13]:

$$C_{FD} = C_T - 0.015 \cdot A \qquad \text{(Eq. 3)}$$

where C_T is the measured total Ca^{2+} in dialysate and A is the albumin concentration in dialysate (2 g/L).

In the transport calculations, the plasma-ionized Ca^{2+} concentration was corrected using the Donnan factor for a divalent cation (0.96^2). "Freely diffusible" Ca^{2+} in plasma (C_{FP}) was almost identical to that which could be extrapolated from diffusible Ca^{2+} in the dialysate plotted as a function of time [$C_{FD}(t)$]. The time-courses of C_{FD} (or ionized dialysate Ca^{2+}, C_{ID}) were modeled with *arbitrary* multiexponential functions:

$$C_{FD}(t) = C_{FP} + B \cdot e^{-k_C \cdot t}$$

For ionized Ca^{2+} C_{FD} was substituted by $C_{ID}(t)$ and C_{FP} by C_{IP}. The calculated arbitrary parameters B, k_B, C, k_C, have no functional meaning and were not used for subsequent analyses.

Calcium gain (ΔM) was calculated from simple mass balance principles:

$$\Delta M = V_{in} \cdot C_{in} - V_{out} \cdot C_{out} \qquad \text{(Eq. 4)}$$

where V_{in} and V_{out} represent instilled and drained volumes, respectively, and C_{in} and C_{out} represent initial solute (Ca^{2+}) and drained solute (Ca^{2+}) concentrations in the dialysate, respectively. At time zero, C_{out} is modified in a step-change fashion due to the presence of residual volume (~300 mL) containing Ca^{2+}, which is in equilibrium with plasma-ionized Ca^{2+}. Thus, by necessity, a step change in ΔM will occur at $t = 0$, whenever the dialysis fluid Ca^{2+} differs from the residual volume Ca^{2+} (equaling the corrected plasma Ca^{2+} at equilibrium). ΔM as a function of time [$\Delta M(t)$] was described by:

$$\Delta M(t) = V_{in} \cdot C_{in} - [V(t) - V_R]C(t) \qquad \text{(Eq. 5)}$$

where V(t) and C(t) represent intraperitoneal volume and solute concentration as a function of time, respectively, whereas V_R represents the residual volume calculated from RISA dilution (see below).

The indicator dilution technique was used to determine the intraperitoneal volume as a function of time [V(t)] using RISA as the dilution marker and correcting for RISA disappearance during the course of the dwell [14, 15]. It was assumed that RISA disappearance occurred due to a largely mono-exponential decay and that the initial binding of RISA was 4% of the instilled mass of RISA [15]. The amount of RISA remaining in the residual volume was accounted for by making an extra exchange (rinse exchange) directly following upon the standardized dwell, which recovered 90% of the residual interperitoneal RISA content from the previous dwell.

The clearance of RISA from dialysate to plasma (Cl → P), corrected for spill over from plasma to interstitium, and the total clearance of RISA (Cl) out of the peritoneal cavity (to the peritoneal tissues) were calculated as described previously, based on peritoneal RISA kinetics [14, 15]. In order to calculate Cl → P, plasma volume was approximately estimated from tabulated data on body weight, height, and gender and by converting "central hematocrit" to "whole body hematocrit." "Spill-over" correction (of Cl → P) for RISA transport from plasma to interstitium was made assuming a "transcapillary escape rate" (TER) of albumin of 5%/hour.

For computer simulations and parameter estimations of solute and fluid transport, the three-pore model of peritoneal transport was employed setting the small-pore radius at 43 Å, the large-pore radius at 250 Å, the fractional small-pore ultrafiltration coefficient (α_S) at 0.9, the fractional transcellular ultrafiltration coefficient (α_C) at

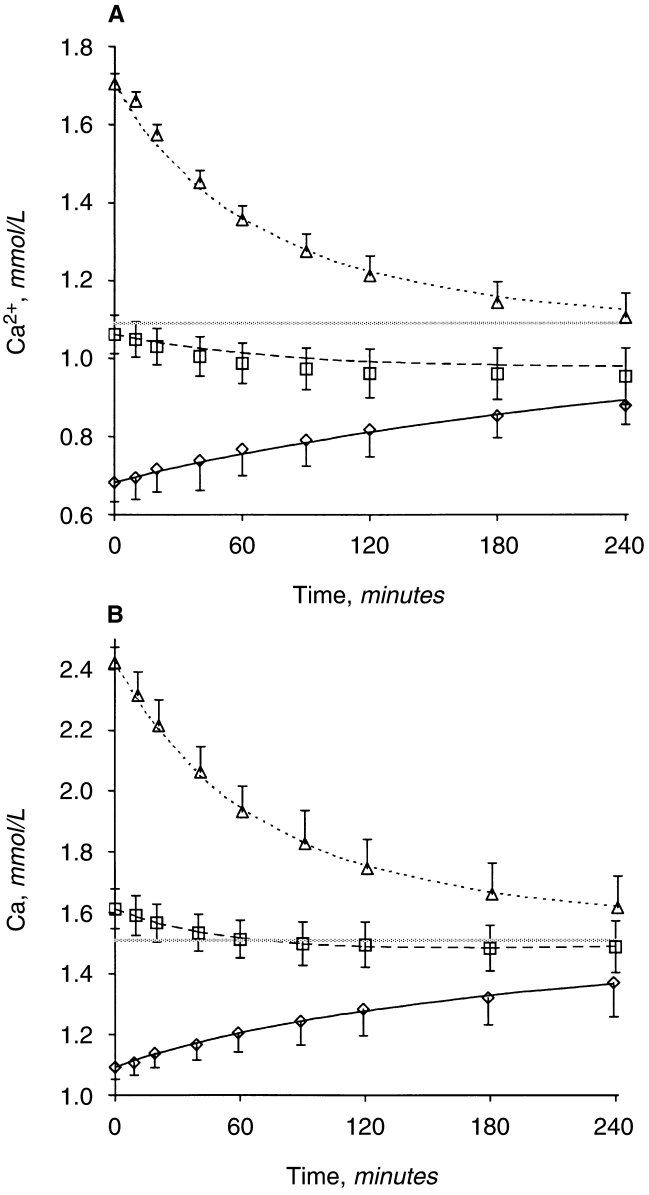

Fig. 1. Dialysate Ca^{2+} as a function of dwell time. (*A*) Ionized dialysate Ca^{2+} as a function of dwell time. (*B*) Total "diffusible" dialysate Ca^{2+} as a function of dwell time. Dotted curves (△) represent the 3.9% glucose solution, hatched curves (□) the 2.5% glucose solution, and solid curves (◇) the 1.5% glucose solution. The gray lines correspond to the average plasma levels of diffusible Ca^{2+} and ionized Ca^{2+}, respectively. Note that the ionized dialysate Ca^{2+} concentration curve is aiming at a value considerably lower than the plasma concentration. The same phenomenon, although less pronounced, is observed for freely diffusible Ca^{2+} (B).

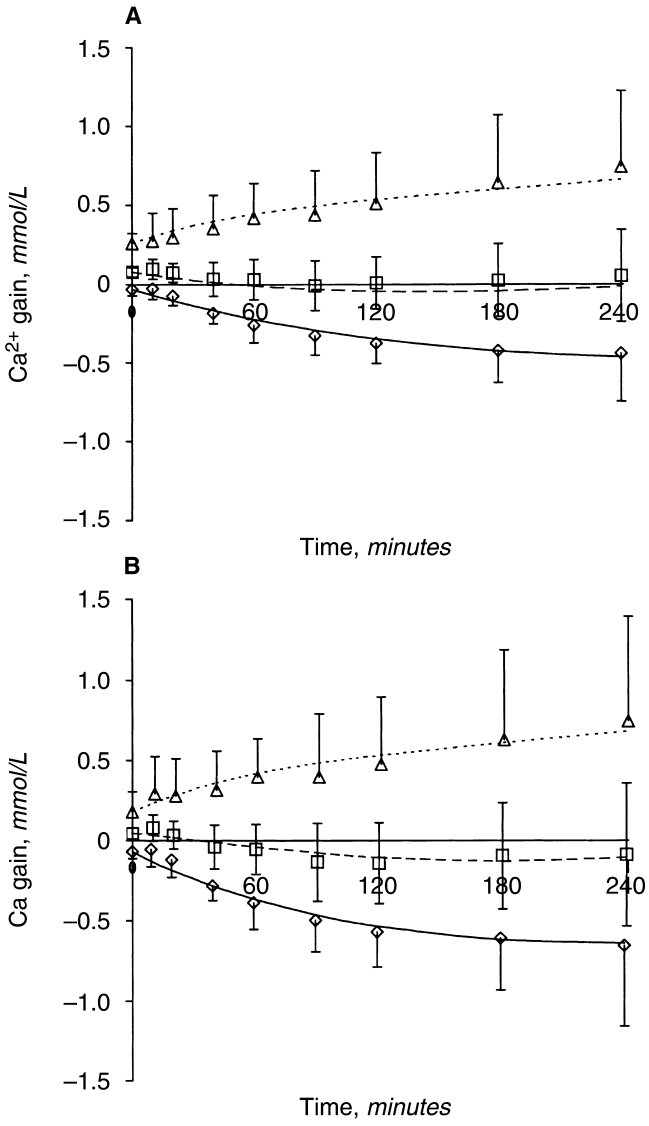

Fig. 2. Gain of Ca^{2+} as function of dwell time. (*A*) Gain of ionized Ca^{2+} as a function of dwell time [ΔM(t)]. (*B*) Gain of total "diffusible" Ca^{2+} as a function of dwell time. Dotted curves (△) represent the 3.9% glucose solution, hatched curves (□) the 2.5% glucose solution, and solid curves (◇) the 1.5% glucose solution. Simulations are made according to the three-pore model and setting the permeability-surface area product (PS) for ionized Ca^{2+} at the values given in Table 2. For diffusible Ca^{2+} (calculated according to equation 2), PS values, not unexpectedly, showed large variation. For the 1.5% glucose solution, Ca^{2+} PS was 13.81 ± 5.10 mL/min, for the 2.5% glucose solution, Ca^{2+} PS was 24.10 ± 8.21 mL/min, and for the 3.9% G solution Ca^{2+} PS was estimated to 17.68 ± 4.57 mL/min.

0.02, and the ultrafiltration coefficient at 0.074 (mL/min/mm Hg). An estimate of the "unrestricted pore area over unit diffusion distance" ($A_0/\Delta X$) was based on PS values for glucose, lactate, creatinine, urea, bicarbonate, and phosphate, assuming the pore radii and fractional hydraulic conductances given above. To calculate the restriction coefficient for diffusion restriction across cylindric pores (A/A_0) and the solute reflection coefficient (σ) the formulations by Mason, Wendt, and Bresler [16] were used.

Concerning simulations of ultrafiltration, there has to date been no methods available to simulate ultrafiltration curves by single membrane formalism by employing *measured* values for PS for glucose and values for direct lymphatic absorption. The reason is that the apparent osmotic gradient across the capillary walls seems to dis-

Table 2. Measured and predicted mass transfer area coefficients (PS) in mL/min (means ± SD) for some of the nonelectrolytes and ions assessed

	Nonelectrolytes			Cations		Anions		
	Urea	Creatinine	Glucose	K^+	Ionized Ca^{2+}	Lactate	Bicarbonate	Phosphate
SE-radius *Å*	1.8	3.0	3.66	2.0	2.2	2.35	2.05	2.77
PD-fluid glucose concentration %								
1.5	20.3 ± 3.1	9.5 ± 2.5	8.9 ± 3.2	16.6 ± 2.7	8.06 ± 1.9[a]	14.1 ± 7.6	22.0 ± 7.0	13.3 ± 13.6
2.5	24.5 ± 4.4	11.1 ± 1.8	9.3 ± 1.5	18.4 ± 2.6	5.44 ± 0.73[b,c]	13.0 ± 2.4	21.5 ± 3.0	7.6 ± 1.8
3.9	23.5 ± 5.0	10.9 ± 1.9	9.9 ± 1.7	16.6 ± 6.5	16.8 ± 6.38	14.4 ± 3.6	20.8 ± 4.8	7.3 ± 2.9
Predicted PS $A_0/\Delta X$ = 23,600 *cm*	21.74	11.50	8.79	19.16	17.05	15.77	18.60	12.77

Abbreviations are: SE, Stokes-Einstein; PS, permeability-surface area product.
[a] Significantly lower than that for 3.9% glucose, $P < 0.01$
[b] Significantly lower than that for 1.5% glucose, $P < 0.01$ and 3.9% glucose, $P < 0.001$
[c] Significantly lower than that for 3.9% glucose, $P < 0.001$

appear much faster than the "macroscopic" glucose concentration gradient between dialysate and (peripheral vein) plasma. The major cause of this discrepancy is probably that, over dwell time, glucose gradients gradually build up in the interstitium, so as to make the effective glucose concentration outside the capillary wall much lower than that measured in the dialysate. One way of accounting for this rapid apparent disappearance of the (glucose) osmotic gradient is to artificially "inflate" PS for glucose to ~15 mL/min [8–12]. However, in the present study, in order to *arbitrarily* simulate volume curves over a limited period of time, apparent lymphatic absorption was instead increased to around 2 mL/min, while retaining glucose PS at measured value (averaging 9.8 mL/min). With this maneuver volume curves could be simulated for the short dwell times in the present study (4 hours), but could not be correctly evaluated for longer dwell times, because of the high peritoneal-to-plasma fluid reabsorption occurring for such an "inflated" apparent lymphatic absorption term.

Statistics

Values are given as means ± standard deviations (SD). Differences among groups were analyzed using analysis of variance (ANOVA). Differences were tested using Student *t* test and Bonferroni post hoc analysis. To fit computer-simulated curves (according to the three-pore model) to measured data, a nonlinear least squares regression analysis was performed. A Bland and Altman analysis [17] was performed to test the agreement of measured PS values (for calcium) with the theoretically predicted PS values using the individually assessed $A_0/\Delta X$ for each patient.

RESULTS

Eight patients carried out all transport studies. No complications occurred in any patients during the study.

Figure 1A shows the dialysate ionized Ca^{2+} as a function of dwell time and glucose concentration, and also (Fig. 1B) the freely diffusible Ca^{2+} in the dialysate as a function of time. Average plasma levels of ionized Ca^{2+} and of freely diffusible Ca^{2+} are also indicated. Note the markedly different concentrations of "ionized" and "freely diffusible" Ca^{2+}, respectively, where the latter concentration is approximately 0.4 mmol/L higher than the former. Note also that the dialysate ionized Ca^{2+} curve apparently is aiming at an equilibrium concentration slightly below 1.0 mmol/L, which is lower than the plasma concentration multiplied by the Donnan factor (0.96^2). A similar tendency was seen for the freely diffusible Ca^{2+} concentration curve, although it here appeared less prominent.

Figure 2 shows the gain as a function of dwell time [$\Delta M(t)$] of ionized and freely diffusible Ca^{2+}, respectively, across the peritoneum for the three different glucose solutions and the corresponding Ca^{2+} concentrations. With respect to the ionized Ca^{2+} gain, the best fitting curves (according to the three-pore model) was for PS = 8.06 ± 1.9 mL/min for the 1.5% glucose, whereas PS was 5.44 ± 0.73 mL/min for the 2.5% glucose, and 16.8 ± 6.38 mL/min for the 3.9% glucose solution. Thus, for the situation where the concentration gap between the initial dialysate Ca^{2+} and plasma water Ca^{2+} was less than 0.4 mmol/L, then the PS for Ca^{2+} was found to be abnormally low. However, when the initial gap between dialysate and plasma Ca^{2+} was high, as for the 3.9% glucose, then the measured PS was consistent with that predicted by the three-pore model. Based on measured data, we could simulate that 1.38 mmol/L Ca^{2+} in the dialysis fluid would have created zero net peritoneal Ca^{2+} gain during a 4-hour dwell for 1.5% glucose, whereas 1.7 and 2.2 mmol/L Ca^{2+} would have been needed to produce zero Ca^{2+} gain for 2.5% glucose and 3.9% glucose (during 4 hours), respectively.

The PS values for urea, creatinine, glucose, potassium, Ca^{2+}, lactate, bicarbonate and phosphate are given in Table 2. In the table the solutes are categorized as "nonelectrolytes," "cations," or "anions." Predicted PS values according to the three-pore model, calculated for an $A_0/\Delta X$ of 23,600 cm (the measured average was 23,594 ± 4697 cm), are also shown. Note that predicted PS values

are consistent with measured values for urea, creatinine, glucose, potassium, lactate and bicarbonate, and reasonably close to measured values for phosphate. However, predicted and measured PS products differed markedly for Ca^{2+} for 1.5% and 2.5% glucose, respectively.

The internal consistency of measured and predicted (computer-simulated) PS values was high for 3.9% glucose as shown by a Bland and Altman analysis (Fig. 3C). However, for 1.5% glucose and 2.5% glucose there was a marked deviation of measured PS vs. predicted PS values based on the $A_0/\Delta X$ values individually determined using the three-pore model in each patient (Fig. 3 A and B). This further emphasizes the discrepancies shown in Table 2.

Total clearance of RISA out of the peritoneal cavity (Cl) and the "direct" lymphatic absorption (Cl → P) for the three different solutions were all similar for the solutions tested (i.e., 2.04 ± 1.71 (± SD) mL/min and 0.16 ± 0.15 mL/min, respectively). The great discrepancy between Cl and Cl → P is consistent with previous measurements in patients by our group [18] and by others [19–21].

DISCUSSION

The major result of the present study is that our previous computer simulations and predictions concerning a marked ultrafiltration dependence of Ca^{2+} transport in CAPD patients was confirmed. Thus, for current conventional peritoneal dialysis solutions, with dialysis fluid Ca^{2+} of the order of 1.25 to 1.30 mmol/L, a markedly negative peritoneal Ca^{2+} balance can be predicted for a 3.86% glucose solution, whereas the peritoneal Ca^{2+} balance can be predicted to be close to "neutral" for a 1.3 to 1.5% glucose solution, as confirmed in the present study. Second, it was for the first time possible to calculate an apparent mass transfer area coefficient (PS) for ionized Ca^{2+}, both under conditions when the concentration gradient between dialysis fluid Ca^{2+} and plasma Ca^{2+} was low, as is usually the case, and under conditions when this gradient was high, namely for 3.9% glucose and 2.5 mmol/L Ca^{2+}. Similar to the situation for sodium, PS for Ca^{2+} was abnormally low when the concentration gap between plasma and dialysate was small, but increased to values predictable by the three-pore model when the gap was relatively high (≥0.7 mmol/L).

The present study emphasizes the fact that peritoneal transport processes for electrolytes markedly differ from those of non-electrolytes. This is particularly obvious when the ion concentration gradient between plasma and dialysate is low. Hence, at dialysate sodium concentrations close to plasma concentration, or even up to 30 to 40 mmol/L lower than the plasma sodium concentration, PS for sodium has been calculated to be of the order of 6 to 9 mL/min in humans [22–27]. At extremely low intraperitoneal sodium concentrations (~50 mmol/L),

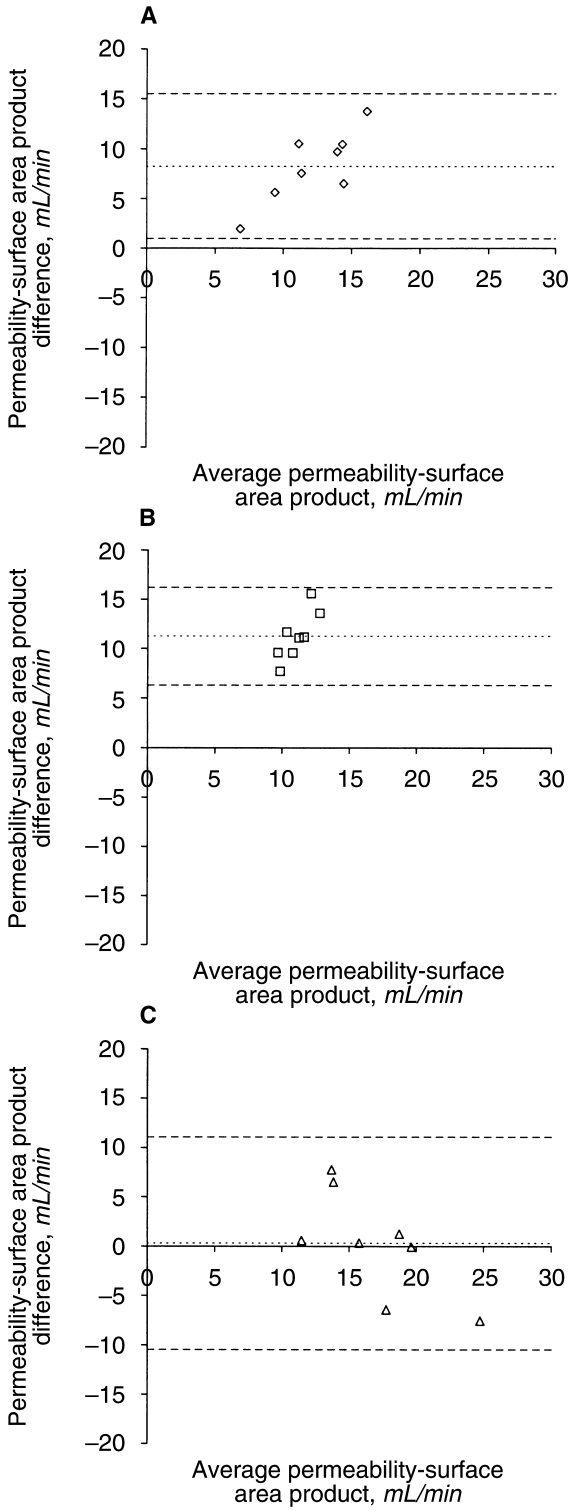

Fig. 3. Bland and Altman plots of the difference between measured the permeability-surface area product (PS) for ionized Ca^{2+} and computed PS for Ca^{2+} (using the three-pore model and the individually determined $A_0/\Delta X$ for each patient) vs. average PS for 1.5% glucose (*A*), 2.5% glucose (*B*), and for 3.9% glucose (*C*). Dotted lines indicate measured averages and hatched lines ±95% confidence intervals. There was an almost perfect agreement between measured and computer-simulated PS values for 3.9% glucose, while there were large overestimations of PS (~10 mL/min) using the three-pore model for 1.5% and 2.5% glucose solutions, respectively.

Table 3. Phenomenologic equations describing membrane transport of nonelectrolytes and charged solutes

Phenomenologic equations describing membrane transport of nonelectrolytes [33]
Solvent flow = Hydraulic flow + Osmotic flow
Solute flux = Ultrafiltration + Diffusion
Phenomenologic equations describing membrane transport of charged solutes [33]
Solvent flow = Hydraulic flow + Osmotic flow + Electrosmotic flow
Solute flux = Ultrafiltration + Diffusion + Electrophoresis (ion migration)
Current flow = Streaming current + Diffusion current + Electric current

however, PS is more or less normalized (Simonsen, unpublished observations). Likewise, Knochel [28] found that peritoneal transport of sodium in dogs was as fast as the transport of urea and creatinine if the dialysis solution (5% glucose) contained no sodium [28]. This finding was recently confirmed and extended by Cheng et al [29] in rats. The rather "predictable" PS for bicarbonate, potassium, lactate, and phosphate in the present study (Table 2), and also in a number of previous studies [22, 23, 30, 31], are quite in line with this reasoning, because the transperitoneal concentration gradients for these ions are usually quite large. By contrast, MTACs for electrolytes close to their equilibrium plasma (water) concentrations are usually considerably lower than predicted from theory.

It is generally believed that the abnormally low PS values obtained for ions near their equilibrium concentrations may be due to the fact that PS, for mathematical reasons, must become quite inexact due to the low diffusion gradient per se [25]. Furthermore, inaccuracies in the laboratory measurements may produce great errors, which will be further amplified due to the low diffusion gradient. Also, large errors will be made, if the Donnan correction is not correctly carried out, or if "plasma concentration" instead of "aqueous solute concentration" is used in the calculations [32] when a flame photometer instead of ion-selective electrodes is used for assessing ion concentrations. Still, during a single dwell, even if the ion concentration gradient between plasma and dialysate is initially quite close to equilibrium, as is normally the case for sodium, the concentration gradient may increase markedly over the course of the dwell [27]. Thus, other explanations may have to be sought.

The anomalous PS values to ions are most likely due to the fact that equations for nonelectrolytes, a priori, should not be expected to apply for ions. In order to correctly describe ion transport, nonelectrolyte transport equations describing diffusion and convection (solute transport) as well as hydraulic flow and osmosis (fluid transport) have to be supplemented with additional terms. The solute flux equation has to be supplemented with an "electrophoresis" (or "ion migration") term, and the fluid flow equation by an "electroosmotic flow" term. Furthermore, a new set of equations describing "current flow" (consisting of "streaming current," "diffusion current," and "electric current") has to be added [33] (Table 3). Moreover, for a single membrane system, solute permeability (P), membrane hydraulic conductivity (L_P) and the reflection coefficient (σ) are the practical membrane coefficients necessary to describe transmembrane flux of an uncharged solute. If the solute is charged, however, three new practical coefficients must be included, namely "electric conductance," "transport number," and "electroosmotic permeability" [33]. All these ion-associated "charge-dependent" terms add tremendous complexity to the calculations, not taken into consideration by equations for nonelectrolytes. On the other hand, they are most important when ions are close to their equilibrium concentration, and distort the apparent PS values when calculated using nonelectrolyte equations.

The results from the present study clearly suggest that the "charge-dependent" transport terms discussed above can actually be neglected under the provision that the dialysate and plasma ion concentrations are widely separated, and thus are far from equilibrium. Hence, there was a good concordance between measured and predicted peritoneal PS values for K^+, bicarbonate, lactate and, in essence, to phosphate, all having large initial peritoneal diffusion gradients (see Table 2). However, correct transport formalism may be needed to adequately model ion transport phenomena under equilibrium conditions. Since this was not done in the present study, or in other studies of similar kind [24–27, 29–31], we are left with estimating "apparent" solute PS values for ions like sodium and Ca^{2+} under "ordinary" conditions (i.e., when the dialysate concentration of these ions are close to their equilibrium plasma concentration).

Neglecting the complexity of simulating ion transport across membranes, it was still possible, using simple model approaches, to rather precisely predict ionized Ca^{2+} gain in the present study, assuming that, when dialysate Ca^{2+} was close to plasma Ca^{2+}, PS was low and similar to that of sodium (6 mL/min). Indeed, a marked ultrafiltration dependence of Ca^{2+} was predicted, even though simulated PS to Ca^{2+} had to be increased (to match measured data) when dialysis fluid Ca^{2+} was 2.5 mmol/L. Based on measured data, 1.38 mmol/L Ca^{2+} in the dialysis fluid would have created completely Ca^{2+}-neutral conditions (no net Ca^{2+} gain during 4 hours) for 1.5% glucose, whereas 1.7 and 2.2 mmol/L would have matched 2.5% glucose and 3.9% glucose in this respect, respectively.

CONCLUSION

Transperitoneal Ca^{2+} transport assessed in CAPD patients was found to be markedly ultrafiltration dependent in agreement with previous predictions. Furthermore, nonelectrolyte equations can be used to predict ion transport (Ca^{2+}), provided that the transperitoneal ion concentration gradients are large, curtailing the impact of "charge-dependent" terms in the equations. Finally, during a 4-hour dwell zero net peritoneal Ca^{2+} transport could be predicted to occur for 1.38 mmol/L Ca^{2+} in a 1.5% glucose solution, whereas zero net Ca^{2+} gain was predicted to occur for 1.7 and 2.2 mmol/L Ca^{2+} in 2.5% glucose and 3.9% glucose solutions, respectively.

ACKNOWLEDGMENTS

This study was supported by grants from the Swedish Medical Research Council 08285, a European Union Contract FMRX-CT98-0219, and from Gambro Lundia AB. Special thanks to Lena Krützén at the Home Dialysis Unit, Lund, and Susanne Pedersen and Helen Andersson at Gambro Lundia AB, for carrying out the dwell studies. Kerstin Wihlborg is greatly acknowledged for her skill in typing the manuscript. Parts of this manuscript has been published in abstract form [Simonsen O, Wieslander AP, Rippe B, *J Am Soc Nephrol* 11:219A, 2000; Simonsen O, Wieslander AP, Rippe B, *Perit Dial Int* 21(Suppl 1):S18, 2001; and Simonsen O, Wieslander AP, Rippe B, *Perit Dial Int* 21(Suppl 2):S139, 2001].

Reprint requests to Professor Bengt Rippe, Department of Nephrology, University Hospital of Lund, S-211 85 Lund, Sweden.
E-mail: Bengt.Rippe@njur.lu.se

REFERENCES

1. Kwong MBL, Lee JSK, Chan MK: Transperitoneal calcium and magnesium transfer during an 8-hour dialysis. *Perit Dial Bull* 7:85–89, 1987
2. Delmez JA, Slatopolsky E, Martin K, Gearing B, *et al*: Minerals, vitamin D, and parathyroid hormone in continuous ambulant peritoneal dialysis. *Kidney Int* 21:862–867, 1982
3. Weinreich T, Colombi HH, Echterhoff G, *et al*: Transperitoneal calcium mass transfer using dialysate with a low calcium concentration (1.0 mM). *Perit Dial Int* 13(Suppl 2):S467–S470, 1993
4. Garrett JJ, Cuddihee RE: Calcium absorption during peritoneal dialysis. *ASAIO Trans* 14:372–375, 1968
5. Parker A, Nolph KD: Magnesium and calcium mass transfer during continuous ambulatory peritoneal dialysis. *ASAIO Trans* 26:194, 1980
6. Martis L, Serkes KD, Nolph KD: Calcium carbonate as a phosphate binder: Is there a need to adjust peritoneal dialysate calcium concentrations for patients using $CaCO_3$? *Perit Dial Int* 9:325–328, 1989
7. Hutchinson JA, Merchant M, Boulton HF, Hinchcliffe R, *et al*: Calcium and magnesium mass transfer in peritoneal dialysis patients using 1.25 mmol/L calcium, 0.25 mmol/L magnesium dialysis fluid. *Perit Dial Int* 13:219–223, 1993
8. Rippe B, Levin L: Should dialysate calcium be varied in proportion to the amount of ultrafiltration in peritoneal dialysis dwells? Directions from a computer simulation. *Perit Dial Int* 18:474–477, 1998
9. Rippe B, Stelin G, Haraldsson B: Computer simulations of peritoneal fluid transport in CAPD. *Kidney Int* 40:315–325, 1991
10. Vonesh EF, Rippe B: Net fluid absorption under membrane transport models of peritoneal dialysis. *Blood Purif* 10:209–226, 1992
11. Rippe B, Levin L: Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD. *Kidney Int* 57:2546–2556, 2000
12. Rippe B, Simonsen O, Heimbürger O, *et al*: Long-term clinical effects of a peritoneal dialysis fluid with less glucose degradation products. *Kidney Int* 59:348–357, 2001
13. Nordin BE: Calcium homeostasis. *Clin Biochem* 23:3–10, 1990
14. Rosengren BI, Carlsson O, Rippe B: Hyaluronan and peritoneal ultrafiltration. A test of the "filter-cake" hypothesis. *Am J Kidney Dis* 37:1277–1285, 2001
15. Zakaria ER, Rippe B: Intraperitoneal fluid volume changes during peritoneal dialysis in the rat. Indicator dilution vs. volumetric measurements. *Blood Purif* 13:255–270, 1995
16. Mason EA, Wendt RP, Bresler EH: Similarity relations (dimensional analysis) for membrane transport. *J Membr Sci* 6:283–298, 1980
17. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 8:307–310, 1986
18. Rippe B, Stelin G, Ahlmén J: Lymph flow from the peritoneal cavity in CAPD patients, in *Frontiers in Peritoneal Dialysis* (vol 4), edited by Maher JF, Winchester JF, New York, Field, Rich and Ass, Inc., 1986, pp 24–30
19. Daugirdas JT, Ing TS, Gandhi VC, *et al*: Kinetics of peritoneal fluid absorption in patients with chronic renal failure. *J Lab Clin Med* 95:351–361, 1980
20. Joffe P, Henriksen JH: Bidirectional peritoneal transport of albumin in continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 10:1725–1732, 1995
21. Heimbürger O, Waniewski J, Werynski A, *et al*: Lymphatic absorption in CAPD patients with loss of ultrafiltration capacity. *Blood Purif* 13:327–339, 1995
22. Heimbürger O, Waniewski J, Werynski A, Lindholm B: A quantitative description of solute and fluid transport during peritoneal dialysis. *Kidney Int* 41:1320–1332, 1992
23. Heimbürger O, Waniewski J, Werynski A, *et al*: Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. *Kidney Int* 38:495–506, 1990
24. Wang T, Waniewski J, Heimbürger O, *et al*: A quantitative analysis of sodium transport and removal during peritoneal dialysis. *Kidney Int* 52:1609–1616, 1997
25. Imholz ALT, Koomen GCM, Struijk DG, Arisz L, *et al*: Fluid and solute transport in CAPD patients using ultralow sodium dialysate. *Kidney Int* 46:333–340, 1994
26. Leypoldt JK, Charney DI, Cheung AK, Naprestek C, *et al*: Ultrafiltration and solute kinetics using low sodium peritoneal dialysate. *Kidney Int* 48:1959–1966, 1995
27. Graff J, Fugleberg S, Brahm J, Fogh-Andersen N: Transperitoneal transport of sodium during hypertonic peritoneal dialysis. *Clin Physiol* 16:31–39, 1996
28. Knochel JP: Formation of peritoneal fluid hypertonicity during dialysis with isotonic glucose solutions. *J Appl Physiol* 27:233–236, 1969
29. Cheng HH, Wang T, Heimbürger O, *et al*: Fluid and solute transport using different sodium concentrations in peritoneal dialysis solutions. *Perit Dial Int* 21:65–71, 2001
30. Graff J, Fugleberg S, Joffe P, *et al*: Parameter estimation in six numerical models of transperitoneal transport of potassium in patients undergoing peritoneal dialysis. *Clin Physiol* 15:185–197, 1995
31. Graff J, Fugleberg S, Brahm J, Fogh-Andersen N: The transport of phosphate between the plasma and dialysate compartments in peritoneal dialysis is influenced by an electric potential difference. *Clin Physiol* 16:291–300, 1996
32. Waniewski J, Heimbürger O, Werynski A, Lindholm B: Aqueous solute concentrations and evaluation of mass transport coefficients in peritoneal dialysis. *Nephrol Dial Transpl* 7:50–56, 1992
33. Kedem O, Katchalsky A: Permeability of composite membranes. Parts 1, 2 and 3. *Trans Faraday Soc* 59:1918–1954, 1963
34. Liede DR, Frederikse HPR, in *CRC Handbook of Chemistry and Physics*, edited by Leide DR, Frederikse HPR, Boca Raton, New York, London, Tokyo, CRC Press, 1995