Unrestricted pore area ($A_0/\Delta x$) is a better indicator of peritoneal membrane function than PET

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**Background.** How to measure the peritoneal exchange in uremic patients treated with peritoneal dialysis (PD) is still a matter of controversy. Most clinics use the peritoneal equilibration test (PET), but from a theoretical point of view, it would be more appropriate to determine the “area” parameter, $A_0/\Delta x$. The latter reflects the total unrestricted pore area per centimeter diffusion distance and can be obtained by three-pore analysis using, for example, the PD capacity test (PDC). To evaluate the different estimates of peritoneal function, PET data and the $A_0/\Delta x$ parameters were compared with the independently determined uptake of a small diffusible tracer, iohexol (molecular weight of 821 D), from the abdominal cavity to blood.

**Methods.** Fourteen patients on routine PD underwent determinations of PET and $A_0/\Delta x$ using PDC. Within a month, the two-hour uptake of iohexol (6 mg/mL) was also determined from the plasma iohexol concentration following abdominal filling.

**Results.** A strong correlation was found between the rate of iohexol plasma concentration increase ($k_{30-120}$) and $A_0/\Delta x$ ($r^2 = 0.799; N = 14$) for the 2 L dwell, while the PET data were far less related to iohexol uptake ($r^2 = 0.015$, respectively).

**Conclusion.** The “area” parameter, $A_0/\Delta x$, is superior to the more widely used routine PET as an indicator of peritoneal membrane function. In addition, the concept of $A_0/\Delta x$ has the virtue of supplying quantitative information about the peritoneal pathophysiology and physiology.

After the initial description of continuous ambulatory peritoneal dialysis (CAPD) [1], this life-supporting therapy has become increasingly popular for patients with chronic renal failure [2]. Worldwide, approximately 15% of the patients needing renal replacement therapy are treated with peritoneal dialysis (PD) [3], but there is a great variation in the PD frequency among different countries. In most studies, the long-term patient mortality and morbidity of PD have been shown to be similar to that of hemodialysis (HD) [4, 5], even though PD is still associated with a higher rate of technique failures than HD [4, 6]. Therefore, considerable interest has been focused on infectious complications [3], long-term durability of the peritoneal membrane [7, 8], dialysis adequacy [3, 9], and metabolic side effects, such as hyperglycemia, hyperlipidemia, and hypoalbuminemia [10]. Indeed, a markedly reduced incidence of peritonitis together with improvements of the technical devices and PD solutions has contributed to enhancement of its long-term technique survival [11–16].

The effort to measure and individualize the dialysis dose is another important factor that contributes to the improved clinical outcome of PD. Hence, it was recognized early that there are large differences between individual patients treated with PD regarding the exchange of solutes and fluid [17]. Moreover, there is no evident relationship between the peritoneal capacity for dialysis and external measurable variables, such as age, gender, body weight, and/or body surface area. Different methods have therefore been introduced and aimed at estimating the PD capacities of individual patients. The most widely used technique is the peritoneal equilibration test (PET) [18], which utilizes the dialysate over plasma (D/P) concentration ratios for urea, creatinine, and the D/D0 ratio for glucose to estimate peritoneal function. Using a 2 L dwell with an intermediate glucose concentration (22.7 mg/mL) for four hours standardizes the conditions. There is also computer software that is based on PET data. Another approach to evaluate the functional properties of peritoneum is to apply the personal dialysis capacity (PDC) test, which is based on a three-pore analysis of the peritoneal membrane [19]. Few attempts have been made to evaluate the possible medical advantages of using one technique rather than the other, even though most clinics routinely follow the peritoneal
exchange as part of their quality control of patients on PD. We do know that the patients that are classified as “high transporters” using PET statistically have increased risks for morbidity and mortality [20]. The reasons for the association are presently unknown [21], although overhydration is one plausible explanation [22, 23].

The present study was undertaken to evaluate how well the two techniques, PET and PDC, estimate the peritoneal exchange capacity compared with the independently determined uptake of a small diffusible tracer, iohexol, from the abdominal cavity to blood.

METHODS

Study group

Fourteen patients, 1 woman and 13 men (age 63 ± 3.7 years, body weight 78 ± 2.8 kg), with end-stage renal disease and who were on maintenance PD (treatment duration 19 ± 3 months) participated in the investigation, which was approved by the ethical committee of Göteborg University (Göteborg, Sweden). All patients were recruited from the Sahlgrenska University Hospital, and they gave their written informed consent before entering the study. The underlying disease of the uremic condition showed the panorama that is common in a dialysis population, and each patient was regarded to be in a stable clinical condition during the time period of the study. The patients were selected to represent a wide range of peritoneal function (discussed in the Results section).

Study protocol

Iohexol uptake technique. The study protocol included two dwells in a crossover fashion on separate days, with dialysate volumes of 0.5 and 2 L, respectively. Each study session started with filling of fresh dialysate fluid (1.5 to 2.5% glucose) containing the tracer iohexol. Venous blood samples for analyses of iohexol were repeatedly taken immediately before the start of filling and during the subsequent two-hour dwell period at 30, 60, 90, and 120 minutes (N = 5). Thereafter, the abdomen was drained, and the patient was returned to his or her ordinary PD protocol.

Tracer. Standard dialyzates were used, and iohexol (300 mg/mL; Omnipaque®, Nycomed, Sweden) was added to reach a concentration of 6 mg/mL (40 mL Omnipaque® to 2 L and 10 mL to the 0.5 L dialysate volume, respectively).

Iohexol is a nonionic x-ray medium with a molecular weight of 821 D. Normally, it is eliminated from plasma in intact form by glomerular filtration (extrarenal clearance of approximately 2 mL/min) [24], but it is also removed by dialysis [25–27]. Iohexol clearance has, in some clinics, become the routine method for determination of the glomerular filtration rate, and there are no indications that iohexol influences the renal function per se [28, 29].

Iohexol concentrations in plasma were analyzed by high-performance liquid chromatography (HPLC) [30]. Also, the dialysate iohexol concentration was analyzed immediately before and directly after the PD exchange.

Calculations. A small but significant background activity in plasma was subtracted from the iohexol concentrations. Moreover, the concentrations were divided by the initial concentration of iohexol in the PD fluid to correct for small variations in dose. For each patient and dialysis session, the linear regression slope was calculated for the relationship of the plasma iohexol concentration versus time. The start of dialysate filling was defined as time zero. The linear regression slope in the time interval 30 to 120 minutes (k_{30-120}) was subsequently related to the A_0/D_x from the PDC test of each patient.

Functional characteristics of the peritoneal membrane

For each patient, the PDC test was determined within a four-week period to the experimental dialysis sessions. The computerized PDC program allowed for an assessment of the functional peritoneal capacity for dialytic exchange based on the three-pore concept for transcapillary exchange [19]. PDC is described by three physiological parameters: (1) the “area parameter” or the unrestricted pore area per centimeter (cm) of diffusion distance (A_0/D_x), which determines the diffusion of small solutes and the hydraulic conductance of the membrane (LpS); (2) the JvAR, which is the final reabsorption rate of fluid from the abdominal cavity to blood when the glucose gradient has dissipated; and (3) the plasma loss (JvL) that determines the loss of proteins from blood to the abdominal cavity through the large pores.

The PET was based on a four-hour exchange with 2 L of 2.27% (or 2.5%) glucose solution. The D/P ratios for urea and creatinine were calculated together with the dialysate glucose concentration at four hours over the initial concentration (D/D_0). The creatinine concentrations were corrected for the interference with glucose using the following Jaffe correction:

$D_{[\text{creat}]}_{\text{true}} = D_{[\text{creat}]}_{\text{measured}} - 0.285 \cdot D_{[\text{glucose}]}

where the correction factor of 0.285 was independently determined by us and valid for our laboratory.

Statistical methods

Results are presented as means ± SE. Linear regression analysis (r = Pearson’s correlation coefficient, d.o.f. = degrees of freedom) was performed where appropriate.

RESULTS

Fourteen patients participated in two experimental PD sessions with dialysate dwell volumes of 2 and 0.5 L
and dialysate iohexol concentrations of 6.02 ± 0.04 and 5.99 ± 0.00 mg/mL, respectively (P = NS). No adverse events occurred during or between the PD sessions. The 0.5 L PD dwell gave fill volumes of 258 ± 6 mL/m² or 6.6 ± 0.3 mL/kg, whereas the 2 L dwell gave fill volumes of 1030 ± 23 mL/m² or 26.2 ± 1.1 mL/kg.

Basic PET data

The dialysate over plasma concentration ratio for urea (D/P urea) after four hours with 2 L of 2.27 or 2.5% glucose intraperitoneally was 0.878 ± 0.011 (range 0.793 to 0.961). D/P for creatinine was 0.629 ± 0.023 (range 0.516 to 0.783), and D/D₀ for glucose was 0.319 ± 0.012 (range 0.229 to 0.387).

The unrestricted pore area, A₀/Δx, from PDC

The average unrestricted pore area over diffusion distance, A₀/Δx, as determined by the PDC test, was 18,800 ± 1270 cm²/cm/1.73 m² BSA, with a range of 11,400 to 26,500. The corresponding A₀/Δx for the 0.5 L volume was 4800 ± 490 cm²/cm/1.73 m² BSA (range 1800 to 7500). The distribution was not random since patients were selected on the basis of previous PDC tests in order to represent a broad spectrum of peritoneal capacities.

Rate constant for iohexol uptake

Figure 1 shows the plasma concentration of iohexol against time after the start of the abdominal fill. The rate constant for iohexol uptake (k₃₀₋₁₂₀) was 0.267 ± 0.015 min⁻¹ (range 0.170 to 0.368) for 2 L of intraperitoneal fill volume and 0.084 ± 0.006 min⁻¹ (range 0.043 to 0.119) for 0.5 L dialysate volumes.

Relationship between A₀/Δx and iohexol uptake

Linear regression analysis of A₀/Δx determined by the PDC test and the rate constant for iohexol uptake after a 2 L PD dwell gave the following relationship: A₀/Δx = 76,300 · k₃₀₋₁₂₀ − 1.56, r² = 0.799, and hence a Pearson’s correlation coefficient of 0.894 (N = 14; Fig. 2). This equation was used to convert the rate constant for iohexol uptake to A₀/Δx for 2 L and 0.5 L PD dwells. Such analysis revealed that the effective A₀/Δx is considerably smaller with the low fill volume of 0.5 L compared with that of 2 L (Fig. 3).

Relationship between PET data and iohexol uptake

The relationship between the PET data and the rate constant for iohexol uptake is demonstrated in Figure 4. The correlation between D/P urea and k₃₀₋₁₂₀ gave the following regression equation: D/P urea = 0.458 · k₃₀₋₁₂₀ + 0.755 (r² = 0.409). The corresponding regression equations for D/P creatinine and D/D₀ glucose were 0.957 · k₃₀₋₁₂₀ + 0.373, r² = 0.436, and D/D₀ glucose = −0.094 · k₃₀₋₁₂₀ + 0.344 (r² = 0.015), respectively (Fig. 4).

DISCUSSION

The hypothesis of a relationship between the peritoneal capillary uptake of a tracer and the functional peritoneal area available for dialytic exchange (A₀/Δx) could be confirmed by the results of the present study. Thus, for the larger dwell volume (2 L), there was a strong correlation between the rate of plasma iohexol concentration increase and the functional peritoneal area assessed by PDC measurements, while the PET data were far less related to the iohexol uptake.

The study included patients with PD as their maintenance renal replacement therapy, and they have routinely performed PDC measurements. They were selected to represent a spectrum of different functional peritoneal capacities (Fig. 1). The standard curve calculated for the area parameter versus plasma iohexol con-
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Fig. 2. Unrestricted pore area per cm diffusion distance (A₀/Δx) as determined by a three-pore analysis of a peritoneal dialysis capacity (PDC) test plotted against the relative rate of plasma concentration increase, k30-120, after intraperitoneal administration of iohexol in 2 L of PD fluid. The linear regression analysis gave the following relationship: A₀/Δx = 76300 · k30-120 - 1.56 (r² = 0.799, N = 14).

Fig. 3. The rate of the increase in plasma concentration (k30-120) after an intraperitoneal administration of iohexol can be converted to A₀/Δx using the relationship in Figure 2. This graph illustrates such A₀/Δx values calculated from the rate constant for iohexol uptake against the individual fill volume (mL/kg, N = 14) for the 0.5 and 2 L PD dwells, respectively. The A₀/Δx is significantly increased after application of the larger fill volume. Also shown is the line of identity.

centration should thereby be representative for varying characteristics of the peritoneal membrane. The strong correlation between k30-120 and A₀/Δx for the 2 L PD solution validates the three-pore concept as used in the PDC program [19]. Thus, if the total pore area available for exchange (per cm of diffusion distance, A₀/Δx) is known, it is possible to estimate the transperitoneal passage for any solute. In the present study, the uptake of iohexol was found to be in direct proportion to the A₀/Δx, at least for the 2 L exchange. For 0.5 L of PD fluid, the relationship was less reliable. Hence, it seems important to use adequate dwell volumes for studies of iohexol uptake after an intraperitoneal injection.

The lower dwell volume of 0.5 L is probably not sufficient to be evenly distributed in the abdominal cavity. Thereby, the peritoneal area available for exchange of solutes and fluid is only partially utilized, to varying degrees in different patients. The k30-120 value of 0.10 for the 0.5 L intraperitoneal volume would suggest that on average only 35 to 40% of the “area” is utilized compared with the 2 L solution. This probably explains why a small intraperitoneal volume is not reabsorbed as fast as expected based on the “area” parameter determined using “normal” abdominal fill volumes.

The intermediate-sized molecule iohexol seems to be a useful marker of the peritoneal exchange when a sufficient dwell volume is used. This is in analogy with results from a recent study in patients with end-stage renal disease and HD treatment where iohexol was found to be a representative tracer for the capillary exchange of solutes in the dialytic situation [31].

For patients with end-stage renal failure, it would be
Fig. 4. (A) Dialysate over plasma (D/P) concentration ratios for urea after four-hour dwells with 2 L of 2.27% glucose solutions plotted against the rate constant for iohexol uptake ($k_{30-120}$). $D/P_{\text{urea}} = 0.458 \cdot k_{30-120} + 0.755$ ($r^2 = 0.409, N = 14$). (B) $D/P_{\text{creatinine}}$ plotted against the rate constant for iohexol uptake ($k_{30-120}$). Linear regression analysis gave the following relationship: $D/P_{\text{creatinine}} = 0.957 \times k_{30-120} + 0.373$ ($r^2 = 0.436, N = 14$). (C) $D/D_0_{\text{glucose}}$ versus the rate constant for iohexol uptake ($k_{30-120}$) yielded the following regression analysis: $D/D_0_{\text{glucose}} = -0.094 \cdot k_{30-120} + 0.344$ ($r^2 = 0.015, N = 14$).
useful to assess the peritoneal functional characteristics before maintenance PD is started. However, the present study shows that 2 L dwell volumes containing iohexol need to be used in order to predict peritoneal function adequately, that is, \( \frac{A}{\Delta x} \). Therefore, the iohexol uptake approach is suitable for patients on PD, but may cause practical problems for those who do not yet have a PD catheter.

The standardized PET is still the most widespread tool for assessment of peritoneal exchange capacity, and variations in PET are often interpreted in terms of “transport” or peritoneal permeability. The changes in dialysate over plasma concentration ratios (D/P, discussed previously in this article) are noteworthy, and hence, PET does not provide clear information of underlying mechanisms in the peritoneal membrane. Factors such as the area available for exchange (\( \frac{A}{\Delta x} \)), the intraperitoneal volume, the rate of “ultrafiltration,” the lymph flow, as well as the pore size and relative pore distribution may all affect the D/P concentration ratios, and therefore the PET results. In accordance with this observation, the PET data of our present study were substantially more scattered and less correlated to the plasma uptake of iohexol than the corresponding PDC results.

The three-pore concept for transcapillary exchange [32], which has been applied to PD [33, 34], offers a basic physiological description of solute and fluid transport in PD. The PDC test is based on the three-pore model and allows for determinations of the transport characteristics of the peritoneal membrane in individual patients [19]. Hence, the PDC has become a useful tool to secure adequate dialysis and to improve the understanding of PD exchange. Furthermore, the PDC parameters have been shown to be reliable as well as highly reproducible and to allow for adequate predictions of the dialysis efficacy in both adults [19] and children [35].

To summarize, we have compared the plasma appearance rate after intraperitoneal administration of iohexol (k_{30-120}) with two other methods of estimating peritoneal function: PET and the area parameter of PDC. The plasma appearance rate of intraperitoneal iohexol is highly correlated to the area parameter (\( \frac{A}{\Delta x} \)) of the PDC test, while PET correlates substantially less to the peritoneal pore area or the k_{30-120}. We conclude that the bluntness of PET as a tool for estimating peritoneal function stands in sharp contrast to its widely spread clinical use.

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**APPENDIX**

*Estimated transperitoneal passage of iohexol*

The final reabsorption rate of fluid from the abdominal cavity to blood, \( J_{\text{vab}} \), is on average 1.2 mL/min. This includes lymph flow and reabsorption across the capillary walls [19]. Assuming that at least 70% of the \( J_{\text{vab}} \) will contain iohexol, a mass transfer area coefficient (MTAC) for iohexol across the peritoneal membrane of 5 mL/min will give a true peritoneal to blood clearance (\( \text{K}_{\text{Gp-p}} \)) of 5.85 mL/min. The MTAC is given by the following expression:

\[
\text{MTAC} = \left( \frac{A}{\Delta x} \right)_x \cdot \left( \frac{A}{A_0} \right)_x \cdot D_{\text{PC}}
\]

(Eq. 1)

where \( \frac{A}{\Delta x} \) is the unrestricted pore area over diffusion distance, \( \frac{A}{A_0} \) is the pore restriction factor for a given solute, and \( D \) is the free diffusion coefficient [19]. Thus, MTAC for a certain solute is directly proportional to the area parameter, \( \frac{A}{\Delta x} \).

*Measured iohexol concentration before and after a two-hour PD dwell*

The iohexol concentrations in the PD fluid were determined before the start of the dwell and after two hours of dialysis, based on the mean of duplicate samples. The initial concentration was close to 6 mg/mL. The concentration of iohexol in the drain solution was corrected for the diluting effects of the estimated residual volume and of the ultrafiltration. The iohexol concentration in the drain fluid was 70.4% (SEM 5.2%, N = 13) of the initial concentration for a fill volume of 2 L, and 57.1% (SEM 5.0%, N = 12) for a fill volume of 0.5 L.

*Calculated iohexol concentration in the dialysate*

Initially, the blood concentration of iohexol is zero, and the intra-peritoneal concentration \( [C_{\text{ip}}(t)] \) is 6 mg/mL. An estimate of the intra-peritoneal concentration at time \( t \), \( C_{\text{ip}}(t) \), can be obtained using the following compartmental analysis:

\[
C_{\text{ip}}(t) = C_{\text{ip}}(0) \cdot e^{-k_{\text{ip}}t}
\]

(Eq. 2)

The expression to the left is the concentration of iohexol in the dialysate at time \( t \) (in minutes) as a fraction of the initial \( C_{\text{ip}} \). Thus, for an intraperitoneal volume \( V_{\text{ip}} \) of 2000 mL, a time \( t \) of 120 minutes and a clearance \( K \) of 4.85 mL/min, the calculated \( C_{\text{ip}}(120) \) would be 70.4%, that is, equivalent to the experimentally determined value. Repeating the calculations for a fill volume \( V_{\text{ip}} \) of 500 mL would give a calculated \( C_{\text{ip}}(120) \) of 24.6%, which is less than half of that experimentally determined. This means that clearance in the situation with a fill volume of 500 mL must be reduced compared with the \( K \) for a \( V_{\text{ip}} \) of 2000 mL.

*Estimating MTAC and \( \frac{A}{\Delta x} \) with a low fill volume*

The total clearance is composed of \( \text{MTAC} + 0.85 \text{ mL min}^{-1} \) (discussed previously in the Appendix), and MTAC is proportional to \( \frac{A}{\Delta x} \). Dividing \( \frac{A}{\Delta x} \) (and hence MTAC) by 3.7 would therefore result in a \( K \) of 2.33 mL/min. Inserting this \( K \), a \( V_{\text{ip}} \) of 500 mL and a \( t \) of 120 minutes into equation 2 results in a \( C_{\text{ip}}(t) \) of 57.0% of the initial intraperitoneal concentration, which is similar to the experimentally determined value. If \( \frac{A}{\Delta x} \) is 18,000 cm²·c m⁻³·s⁻¹ for an intraperitoneal fill volume of 0.5 L. This value is not far from that determined from independent estimates of the uptake of iohexol from the abdominal cavity to blood (discussed in the Results section).

**REFERENCES**