Peritoneal Membrane Transport Function in Children Receiving Long-Term Dialysis

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ABSTRACT
Accurate characterization of peritoneal solute transport capacity in children has been hampered by a lack of standardized test mechanics and small patient numbers. A standardized peritoneal equilibration test was used to study 95 pediatric patients (mean age, 9.9 ± 5.6 yr) receiving chronic peritoneal dialysis at 14 centers. Patients were divided into four age groups (<1, 1 to 3, 4 to 11, 12 to 19 yr) for analysis. Each patient received a 4-h peritoneal equilibration test with an exchange volume of 1100 mL/m² per body surface area. Dialysate to plasma (D/P) ratios for creatinine (C) and urea (U) and the ratio of dialysate glucose (G) to initial dialysate glucose concentration (D/D₀) were determined. Mass transfer area coefficients (MTAC) were calculated for the three solutes and potassium (P). The mean (± SD) 4-h D/P ratios for C and U were 0.64 ± 0.13 and 0.82 ± 0.09, respectively. The mean 4-h D/D₀ for G was 0.33 ± 0.10. D/P and D/D₀ ratio results were similar across age groups. Normalized (for body surface area) mean MTAC (± SD) values were as follows: C, 10.66 ± 3.74; G, 12.93 ± 5.02; U, 18.43 ± 4.02; and P, 14.02 ± 3.94. Whereas a comparison of the normalized MTAC values across age groups with an analysis of variance showed significant age group differences only for glucose (P = 0.001) and potassium (P = 0.036), analysis by quadratic regression demonstrated a nonlinear decrease with age for C (P = 0.016), G (P < 0.001), and P (P = 0.034). In summary, evaluation of D/P and D/D₀ ratios obtained from a large group of children in a standardized manner reveals values that are similar across the pediatric age range and not unlike the results obtained in adults. In contrast, normalized MTAC values of young children are greater than the values of older children, possibly as a result of maturational changes in the peritoneal membrane or differences in the effective peritoneal membrane surface area.

Key Words: Peritoneal dialysis, solute, pediatric, equilibration, permeability

The peritoneal equilibration test (PET) was developed by Twardowski et al. (1) as a means of characterizing solute transport rates across the peritoneum. The construction of reference curves on the basis of the kinetics of solute equilibration between dialysate and plasma (D/P ratio) after a 2-L exchange volume has made possible the simple categorization of adult patients into those with normal, rapid (high and high average) and slow (low and low average) peritoneal solute transport rates, and has become the basis on which to individualize dialysis prescriptions.

The majority of children <15 yr of age with end-stage renal disease receive some form of long-term peritoneal dialysis (2). Nevertheless, perceived differences in peritoneal membrane solute transport characteristics between adults and children have prohibited widespread application of the reference curves of Twardowski et al. to the pediatric dialysis patient (3). Unfortunately, application of the PET to the pediatric dialysis population has also been hampered by the small number of children studied in pediatric protocols and the lack of standardization of dialysis mechanics during the test procedure both within and between studies (4–13).

The mass transfer area coefficient (MTAC) is an additional measure of solute transport capacity and is the most precise means of estimating intrinsic peritoneal membrane permeability and surface area (14,15). As such, it also offers the potential of serving as an additional means of categorizing a patient's peritoneal solute transport rate. However, despite the potential value of this assessment in terms of dialysis prescription, MTAC values have only been reported in a small number of children (16–18).

In response, the Pediatric Peritoneal Dialysis Study Consortium (PPDSC) developed a standardized meth-
odology for conducting a pediatric PET evaluation. The procedure was used to study 95 children \( \leq 19 \) yr of age and has provided solute equilibration curves and MTAC values that can serve as reference data for the pediatric peritoneal dialysis population.

PATIENTS AND METHODS

Ninety-five pediatric peritoneal dialysis patients from 14 centers participated in the cross-sectional study. All patients were cared for in the member institutions of the PPSC (see Appendix). The 95 patients studied had a mean age of 9.9 ± 5.6 yr (range, 0.1 to 19.5 yr), and a mean length of time receiving peritoneal dialysis of 2.0 ± 1.1 yr (range, 0.1 to 4.7 yr). There were 5 (5%) patients \(< 1\) yr, 14 (15%) patients between the ages of 1 and 3 yr, 37 (39%) patients between the ages of 4 and 11 yr, 37 (39%) patients between the ages of 12 and 18 yr, and 2 (2%) patients aged 19 yr. The most frequent primary renal diagnoses were focal segmental glomerulosclerosis (17 patients, 18%), congenital renal hypoplasia/dysplasia (17 patients, 18%), and obstructive uropathy (13 patients, 14%). Overall, the 95 patients studied had a mean body surface area (BSA) of 0.98 ± 0.41 m\(^2\) with minimum and maximum values of 0.23 m\(^2\) and 1.82 m\(^2\), respectively.

A single 4-h PET test was conducted on each patient. The test exchange fill volume was 1100 mL/m\(^2\) BSA and the dialysate solution was 2.5% Dianean© (Baxter Healthcare Corporation, Deerfield, IL), BSA was determined by the method of DuBois and Dubois (19). In each case, the patient had no evidence of peritonitis or had completed antibiotic therapy for peritonitis \(>4\) wk before entering the study.

During the evening before the PET, each patient received a 40 mL/kg exchange (range, 35 to 45 mL/kg) of 2.5% Dianean©, with a dwell time of 8 to 12 h. After arrival at the dialysis unit on the day of testing, the overnight dwell was drained for 20 min with the patient in the sitting position. A transfer set change to a Y-type Dianean© peritoneal dialysis solution administration set was conducted to minimize tubing "dead space" or recirculating volume. The test exchange was conducted next and was infused over 10 min with the patient remaining supine and rolling side to side every 1 to 2 min during the infusion. Dialysate samples were taken from the overnight exchange bag at 0, 30, 60, 120, 180, and 240 min of dwell time from the test exchange volume. Blood samples were drawn at 0 and 240 min. All serum and dialysate samples were centrally analyzed (Baxter Healthcare Corporation, Round Lake, IL) for urea, creatinine, glucose, sodium, and potassium on a Kodak Ektachem 700 machine (Eastman Kodak, Rochester, NY). The Ektachem uses an enzymatic assay method that has no interference with glucose. All serum values were expressed in terms of concentration per volume of plasma water to achieve a physiologically consistent relationship between blood and dialysate concentrations of a particular solute. This was achieved by dividing the serum values by a factor of 0.93, thereby correcting the plasma volume for plasma protein and lipid content (20).

The dialysate to plasma (D/P) ratios for each solute at each sampling time were formed by using the average of the two corrected plasma concentrations in the denominator with the numerator consisting of the dialysate concentration. The D/P ratios for urea nitrogen, creatinine, sodium, and potassium and the ratio of dialysate glucose to initial dialysate glucose concentration (D/D\(_0\)) were calculated in the standard manner (1). There are seven patients whose 4-h dialysate samples are not summarized in this report. All of the patients had 4-h urea and creatinine dialysate values which fell well below the 3-h dialysate value (below 10% of the 3-h value where 10% represents the typical bound on the measurement error of these solutes). Thus, even if near equilibration had already occurred at 3 h, these values fell well below the usual measurement errors associated with urea and creatinine. Consequently, these patients' 4-h values were ignored in all subsequent analyses.

The pre- and post-PET residual peritoneal volume after draining was determined on the basis of creatinine by the formula (21):

\[
\text{Residual volume} = \frac{V_F \times C_{D,0}}{(C_{D,0} - C_D)}
\]

where \(V_F\) is the volume infused for the current exchange, \(C_{D,0}\) is the dialysate creatinine concentration from the end of the previous exchange, and \(C_D\) is the dialysate creatinine concentration immediately after infusion of the current exchange.

The MTAC was calculated for urea nitrogen, creatinine, glucose, and potassium in 83 patients. The calculation of MTAC was excluded in four patients who did not have a preexchange residual dialysate volume determination, one patient who did not have a postexchange residual dialysate volume determination, and the seven patients who were missing D/P values. The determination of MTAC was on the basis of the two-pool model of Pyle-Popovich and was calculated as a weighted average of the following modified two-point (Time 0 and Time t) estimate (15.22,23):

\[
MTAC(t) = \frac{-V_D}{t} \times \ln \left( \frac{1 - D_t}{P} \right)
\]

where \(t\) is time, \(D_t\) is dialysate concentration at Time 0, \(D_t\) is the dialysate concentration at Time \(t\) minutes, \(P\) is the average plasma solute concentration, \(V_D\) is the volume infused plus the preexchange residual volume, \(V_D\) is the drain volume plus the postexchange residual volume, and \(V_D\) is the geometric average of \(V_D\) and \(V_D\). The weights for computing the weighted average are simply the squares of the sampling times, \(t\) such that the overall solute MTAC is then calculated as follows:

\[
MTAC = \left[30^2 \times MTAC(30) + 60^2 \times MTAC(60) + 120^2 \times MTAC(120) + 180^2 \times MTAC(180) + 240^2 \times MTAC(240)\right]/\left[30^2 + 60^2 + 120^2 + 180^2 + 240^2\right].
\]

MTAC values were normalized to BSA with both the DuBois and Dubois and the Haycock formulas (24). In each case, informed patient consent and respective Institutional Review Board approval were obtained before patient participation in this study. Summary statistics are presented in the form of frequencies, means, standard deviations, and minimum and maximum values. Both an analysis of variance (ANOVA) and a quadratic regression analysis were performed to determine whether the normalized MTAC values (according to BSA computed from the DuBois and Dubois formula) differed across the different age groups. The patients were divided into four age groups for analysis to facilitate the detection of any age-related differences in results.
RESULTS

The mean 4-h D/P values for creatinine and urea, and the mean 4-h D/D₀ value for glucose were 0.64 ± 0.13, 0.82 ± 0.09, and 0.33 ± 0.10, respectively. The mean 4-h solute D/P ratios (D/D₀ glucose) by age group are noted in Table 1. There was no statistically significant difference in the values obtained for the different age groups. Solute transport data for all patients as determined by the solute D/P ratios for creatinine and urea and D/D₀ glucose at all time points are presented graphically in Figures 1 to 3. In each case, the solute transport capacity is categorized as high, high average, low average, or low. The categories are defined by the maximum, mean + 1 SD, mean, mean - 1 SD, and minimum D/P and D/D₀ values for the respective solutes.

The mean normalized (to BSA by DuBois and DuBois) (18) MTAC values for creatinine, urea, glucose, and potassium are 10.66 ± 3.74, 18.43 ± 4.02, 12.93 ± 5.02, and 14.02 ± 3.94, respectively. The normalized MTAC data across all ages are presented in Table 2. There was very little difference noted when MTAC values were normalized to BSA by use of either the DuBois and DuBois formula or the Haycock formula (data not shown) (19,24).

To assess whether or not study patients exhibited different membrane characteristics as a function of age and/or peritoneal permeability rather than BSA, normalized (by DuBois and DuBois) (19) MTAC values were compared across selected age groups. Whereas ANOVA demonstrated significant age group differences only for glucose (P = 0.001) and potassium (P = 0.036), a quadratic regression analysis revealed nonlinear decrements of the MTAC with age for creatinine (P = 0.016), glucose (P < 0.001), and potassium (P = 0.034), indicative of a higher peritoneal permeability index or a greater effective peritoneal membrane surface area in the youngest children (Figure 4).

The mean preexchange residual volumes, postexchange residual volumes and ultrafiltration volumes were 189.9 ± 172.5 mL, 215.1 ± 174.3 mL, and 157.7 ± 222.6 mL, respectively. Table 3 presents the summary statistics, by age group, of the mean residual dialysate volumes and ultrafiltration volumes. As noted, both the residual volumes and net ultrafiltration values show considerable variation.

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**TABLE 1. Four-hour solute D/P and D/D₀ ratios**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Creatinine</th>
<th>Urea</th>
<th>Glucose</th>
<th>Sodium</th>
<th>Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0.73 ± 0.07</td>
<td>0.83 ± 0.07</td>
<td>0.20 ± 0.07</td>
<td>0.85 ± 0.07</td>
<td>0.63 ± 0.17</td>
</tr>
<tr>
<td>1 to 3</td>
<td>0.66 ± 0.15</td>
<td>0.83 ± 0.10</td>
<td>0.27 ± 0.09</td>
<td>0.83 ± 0.09</td>
<td>0.72 ± 0.09</td>
</tr>
<tr>
<td>4 to 11</td>
<td>0.65 ± 0.12</td>
<td>0.84 ± 0.06</td>
<td>0.35 ± 0.11</td>
<td>0.85 ± 0.05</td>
<td>0.78 ± 0.07</td>
</tr>
<tr>
<td>12 to 18</td>
<td>0.62 ± 0.13</td>
<td>0.80 ± 0.10</td>
<td>0.34 ± 0.10</td>
<td>0.83 ± 0.07</td>
<td>0.74 ± 0.09</td>
</tr>
<tr>
<td>Total</td>
<td>0.64 ± 0.13</td>
<td>0.82 ± 0.09</td>
<td>0.33 ± 0.10</td>
<td>0.84 ± 0.07</td>
<td>0.75 ± 0.10</td>
</tr>
</tbody>
</table>
capacity in comparison with adult population norms. The information that is obtained has been used to assist the development of an initial individualized peritoneal dialysis prescription or to evaluate the reasons behind the development of inadequate dialysis. However, the results of Twardowski's studies and the adult PET procedure have not been considered applicable to the pediatric dialysis population for two reasons. First, there has been a well acknowledged but unproven perception that the solute transport function of the pediatric peritoneal membrane, especially that of the infant, is different from that of the adult (3). The second reason relates to the size of the test exchange volume. In the "standardized" procedure conducted in Twardowski's study and currently recommended for adult patients, a fixed exchange volume of 2000 mL is used regardless of the body size of the patient. Obviously, this approach does not allow for modification of the exchange volume to reflect differences in body size (e.g., pediatric patient, small adult, large adult) and contributes to the limited usefulness of the Twardowski et al. procedure in children (1,26-28).

Unfortunately, the performance of reproducible peritoneal solute transport studies in pediatrics and an accurate comparison of the results obtained to those of adult peritoneal dialysis patients has historically been hampered by a lack of standardization of dialysis mechanics during the test (4-13). Although procedural factors that must be considered include dialysate inflow, dwell, and outflow times as well as dialysate composition, agreement has been elusive in the past on what should be considered the appropriate scaling factor (e.g., BSA vs. body weight) upon which to base the test exchange volume and interpretation of results (9,30,31).

Direct measurements of the peritoneal membrane by Putlloff (32) and Wegner (33) more than 100 yr ago demonstrated that the peritoneal surface area in infants per unit body weight is actually twice that of the adult, whereas the relationship between BSA and peritoneal membrane surface area is age independent. Accordingly, because the rapidity of solute equilibration between plasma and dialysate is in part dependent on the volume of dialysate into which the dialyzed solute must diffuse, the use of a body weight-based test exchange volume in previous pediatric solute transport studies has merely confirmed the fact that when relatively small dialysate volumes are used in the youngest patients, rapid equilibration is seen and leads to the inaccurate perception of enhanced membrane transport capacity (34). On the other hand, because the relationship between peritoneal membrane surface area and BSA is constant, scaling the test exchange volume by BSA maintains the relationship between dialysate volume and peritoneal membrane surface area across populations; thus, any detectable differences in solute equilibration rates are a result of true differences in peritoneal permeability (9). This concept has recently been confirmed in studies conducted by Kohaut et al. (35) and Warady et al. (36) in association with the PPDS.
TABLE 2. Normalized mass transfer area coefficientsa

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Creatinine</th>
<th>Urea</th>
<th>Glucose</th>
<th>Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>13.47 ± 2.14</td>
<td>19.50 ± 2.47</td>
<td>18.14 ± 4.94</td>
<td>10.24 ± 5.09</td>
</tr>
<tr>
<td>1 to 3</td>
<td>11.39 ± 3.69</td>
<td>19.17 ± 3.40</td>
<td>16.70 ± 5.94</td>
<td>12.71 ± 2.78</td>
</tr>
<tr>
<td>4 to 11</td>
<td>10.88 ± 3.96</td>
<td>19.23 ± 3.99</td>
<td>12.15 ± 4.69</td>
<td>15.28 ± 4.23</td>
</tr>
<tr>
<td>12 to 18</td>
<td>9.78 ± 3.59</td>
<td>17.20 ± 4.34</td>
<td>11.59 ± 3.79</td>
<td>13.93 ± 3.40</td>
</tr>
<tr>
<td>Total</td>
<td>10.66 ± 3.74</td>
<td>18.43 ± 4.02</td>
<td>12.93 ± 5.02</td>
<td>14.02 ± 3.94</td>
</tr>
</tbody>
</table>

a Milliliters per minute, normalized to BSA (DuBois and DuBois formula).

Figure 4. Relationship between corrected (for BSA) mass transfer area coefficient of creatinine (A) and glucose (B) and patient age. MTAC, mass transfer area coefficients.

Peritoneal membrane function, such as the PET, require standardized dialysis mechanics; any deviation from protocol negates accurate comparison of individual data to reference norms (28,36,38). The significant residual dialysate volumes noted as part of the PET evaluation in our patients as well as in the patients of Twardowski et al. (1) and Fukuda et al. (39) may also limit the usefulness of these data. The presence of large residual volumes of dialysate containing solute that has equilibrated with serum during the long overnight dwell could artificially inflate solute D/P ratios, especially during the initial 1 to 2 h of the PET, thereby influencing categorization of solute transport capacity. This is of particular concern when children receive nightly intermittent peritoneal dialysis (NIPD) on the basis of an assessment of peritoneal transport capacity obtained after only short dwell periods (11,12).

The MTAC is a parameter that characterizes the diffusive permeability of the peritoneal membrane. Unlike the D/P ratio, the MTAC is essentially independent of dialysis mechanics (e.g., exchange volume, dialysate dextrose concentration) (16,22). The MTAC has been variably defined as the area available for solute transport divided by the sum of resistances to peritoneal diffusion and represents the clearance rate (expressed in milliliters per minute) which would be obtained in the absence of ultrafiltration or solute accumulation in the dialysate (23). The calculation of the MTAC takes residual volume into account and reflects membrane transport capacity throughout the exchange so that it forms the basis for modeling long dwell (e.g., chronic ambulatory peritoneal dialysis) as well as short dwell (e.g., NIPD) dialysis. The greatest clinical application of the MTAC may be as a means to augment the use of D/P ratios to individualize dialysis prescriptions (26,27,31,36). Although in the past clinicians have been reluctant to use the MTAC to characterize peritoneal membrane solute transport capacity, largely because of the complexity of the calculations involved, computer technology has now made determination of the MTAC much easier (28,40).

Very few prior studies have measured MTAC values in pediatric patients. In the most recent study by Geary et al. (18) in which MTAC values were collected from 28 pediatric patients, solute transport appeared to vary with age and did not approach adult values until later childhood, as was the case in our study. However, the test exchange volume used by Geary et al. (18) was decidedly low (approximately 30 mL/kg) making interpretation of the data and comparison with adult values difficult. In our study, the determination of MTAC values with an exchange volume standardized to BSA in a large number of pediatric patients provides data that permits an accurate assessment of the relationship between peritoneal membrane solute transport function and age. Evaluation of the data with an ANOVA showed differences for glucose and potassium only. In turn, a quadratic regression analysis was performed to safeguard against a possible misclassification of age groups to determine whether there were any linear or nonlinear trends between age and the normalized MTAC values. This analysis confirmed the presence of greater solute
Table 3. Residual dialysate and ultrafiltration volumes

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Preexchange Residual</th>
<th>Postexchange Residual</th>
<th>Ultrafiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>&lt;1</td>
<td>73.4</td>
<td>21.1</td>
<td>60.1</td>
</tr>
<tr>
<td>1 to 3</td>
<td>118.8</td>
<td>152.3</td>
<td>77.9</td>
</tr>
<tr>
<td>4 to 11</td>
<td>150.8</td>
<td>116.4</td>
<td>205.8</td>
</tr>
<tr>
<td>12 to 18</td>
<td>278.0</td>
<td>207.3</td>
<td>302.2</td>
</tr>
<tr>
<td>&gt;18</td>
<td>142.0</td>
<td>19.2</td>
<td>118.9</td>
</tr>
<tr>
<td>Total</td>
<td>189.9</td>
<td>172.5</td>
<td>215.1</td>
</tr>
</tbody>
</table>

*Values are in milliliters.

transport capacity in the youngest patients for glucose, potassium, and creatinine, possibly a result of differences in peritoneal membrane permeability or effective peritoneal surface area. Although one might argue that the clinical impact of this finding is limited because the MTAC reaches the ultrafiltration flow rate, the data does suggest that relatively greater solute clearances might be expected in young children versus adults when dialysis prescriptions are similar.

In summary, this evaluation of the peritoneal membrane solute transport capacity of 95 children receiving long-term peritoneal dialysis conducted with a standardized pediatric PET protocol makes available pediatric reference data in terms of D/P, D/D0, and MTAC values. The information provides evidence that solute transport characteristics of the pediatric population in terms of D/P and D/D0 at 24 hr may be similar to data obtained in adults (1). However, age-related differences in terms of MTAC do exist.

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