Improved Acidosis Correction and Recovery of Mesothelial Cell Mass with Neutral-pH Bicarbonate Dialysis Solution among Children Undergoing Automated Peritoneal Dialysis

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Abstract. Acid-base balance and peritoneal membrane longevity are of utmost relevance for pediatric patients undergoing peritoneal dialysis (PD). PD fluids with neutral pH and reduced glucose degradation product contents are considered more biocompatible, because they preserve peritoneal cell functions in vitro. To investigate the clinical effects of a novel PD fluid buffered with 34 mM pure bicarbonate at neutral pH, a randomized, prospective, crossover comparison with conventional, acidic, 35 mM lactate PD fluid was performed for two consecutive 12-wk periods with 28 children (age, 6 mo to 15 yr) undergoing automated PD (APD). Blood bicarbonate levels and arterial pH were significantly higher after 3 mo of bicarbonate APD (29 ± 15 versus 15 ± 8 U/ml per 4 h, P < 0.01), which is consistent with recovery of the mesothelial cell layer. This effect was fully reversed when the patients returned to lactate fluid. Effluent carcinogen antigen-125 levels were inversely correlated with peritoneal glucose exposure during lactate but not bicarbonate APD, indicating improved in vivo mesothelial cell tolerance of high-dose glucose with the neutral-pH PD fluid with reduced glucose degradation product content. Among children undergoing APD, neutral-pH, bicarbonate-buffered PD fluid provides more effective correction of metabolic acidosis and better preservation of peritoneal cell mass than do conventional, acidic, lactate-based fluids.

Irreversible technique failure remains the major drawback of peritoneal dialysis (PD). Fifty percent of adult and pediatric patients undergoing PD must switch to hemodialysis within 4 to 5 yr (1,2). The incidence of PD failure attributable to infectious complications is steadily decreasing, because of major advances in the prevention and treatment of catheter-related infections, and loss of ultrafiltration and peritoneal sclerosis attributable to noninfectious mechanisms are becoming the leading causes of nonelective termination of PD (1).

An increasing body of experimental evidence supports the idea that the peritoneal hypervascularization and fibrosis observed in long-term PD are causally related to the acute and chronic toxicity of conventional PD solutions (3,4). Low pH, high lactate levels, and hyperosmolar glucose contents independently impair mesothelial cell functions (5–8). The pH of the dialysis fluid might be particularly relevant for automated PD (APD), in which frequent short cycles continuously expose the peritoneal membrane to a cytotoxic acidic milieu (9). Lactate may compromise local cell functions independently of pH by affecting the cellular redox state and reducing cellular energy sources. Furthermore, toxic glucose degradation products are formed during heat sterilization of conventional PD solutions. Glucose degradation products are mostly devoid of acute cytotoxicity but impair the viability and functional integrity of mesothelial cells during extended exposure (10).

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Moreover, glucose degradation products may be directly involved in the pathogenesis of peritoneal hypervascularization and fibrosis, by stimulating local vascular endothelial growth factor (VEGF) and TGF-β synthesis and release (11,12). Finally, glucose degradation products are potent inducers of advanced glycation end product formation, thereby promoting endothelial cell dysfunction, structural alterations of extracellular matrix proteins, and chronic inflammatory reactions in the peritoneum and throughout the body (13).

Recent advances in manufacturing technology have provided the option of separating alkaline and acidic fluid compartments. This permits the sterilization of glucose at very low pH, with greatly reduced glucose degradation product formation, and produces neutral-pH final dialysis solutions, with the use of lactate and/or bicarbonate as a buffer. In addition, the development of novel, gas-tight, plastic bag materials has made it possible to store bicarbonate-based solutions for extended periods.

Fluid biocompatibility is particularly relevant for children with ESRD, because of their potential long-term dependence on a functioning peritoneal membrane and the preferential use of APD, with intense exposure to fresh PD fluids. Moreover, persistent metabolic acidosis is common among children with ESRD (2). Therefore, the use of bicarbonate buffer could confer specific advantages among young children undergoing PD, for whom hepatic conversion of the buffer lactate to bicarbonate is rate-limited (14). Improved correction of metabolic acidosis with bicarbonate-buffered PD fluid has been suggested for adult patients undergoing continuous ambulatory PD (15).

Biocompatible PD fluids buffered with lactate (16–18), bicarbonate (9,15), or a lactate/bicarbonate mixture (19) have recently become commercially available. In this prospective, randomized, crossover trial, we tested the efficacy and biocompatibility of a purely bicarbonate-based, neutral-pH PD solution, in comparison with a conventional, lactate-buffered, acidic fluid.

**Materials and Methods**

**Patients**

The study was performed in six specialized pediatric dialysis units in Germany, Austria, and France. The study was performed in full compliance with the Declaration of Helsinki and the current European Union Good Clinical Practice guidelines for clinical trials. Ethics committee approval for the study protocol was obtained at each center. Written informed consent was obtained from the parents, with assent from the patients. Patients were eligible for the trial if they were younger than 18 yr, were undergoing chronic APD treatment with an average peritoneal fill volume close to 1000 to 1100 ml/m² body surface area, had no severe chronic pulmonary, cardiac, hepatic, or malignant disease, had no history of peritonitis in the previous 3 wk, and exhibited no clinical evidence of major peritoneal adhesions.

Of 34 children recruited for the trial, 28 (including nine girls) were available for randomization at the end of the 1-mo run-in period. The patients were 0.6 to 15.7 yr of age (median, 6.0 yr). At the time of the study, the duration of PD treatment was 1 to 71 mo (median, 13 mo). Thirteen patients had experienced at least one episode of peritonitis. The underlying diseases were focal segmental glomerulosclerosis (n = 4), renal hypoplasia/dysplasia (n = 4), hemolytic uremic syndrome (n = 3), autosomal recessive polycystic kidney disease (n = 3), nephronophthisis (n = 2), diffuse mesangial sclerosis (n = 2), obstructive uropathy, prune belly syndrome, membranoproliferative glomerulonephritis type II, renal venous thrombosis, Denis-Drash syndrome, Schminkle syndrome, and postasphyxia ESRD (each n = 1), and unknown conditions (n = 2). The biochemical profiles of the patients at the time of study entry are presented in Table 1. Of 28 children who began the trial, 24 (13 receiving bicarbonate solution and 11 receiving lactate solution) completed the first 12-wk study period and 16 (seven receiving bicarbonate solution and nine receiving lactate solution) completed the second 12-wk study period. The reasons for discontinuation were transplantation (n = 8), a switch to hemodialysis (n = 1), and the wishes of the family (n = 3).

**Study Design**

The study was performed as an open, randomized, crossover trial. Stable dialysis conditions were ensured with a 4-wk run-in period, during which any oral sodium bicarbonate supplementation was discontinued. The patients then underwent two consecutive 12-wk study periods, in randomized order, in which APD was performed with a neutral-pH PD fluid containing 34 mM bicarbonate (BicaVera 170/180/190; Fresenius Medical Care, Bad Homburg, Germany) or a conventional PD fluid with 35 mM lactate (pH 5.5, CAPD 17/18/19; Fresenius Medical Care). The solutions contained identical concentrations of sodium (134 mM), calcium (1.25 mM), magnesium (0.5 mM), and chloride (102.5 mM), with 15, 23, or 42.5 g/L dextrose. The two treatment phases were separated by a 4-wk washout period with

| Table 1. Acid-base status at baseline and after 12 wk of lactate (n = 20) or bicarbonate (n = 20) dialysis |
|-----------------|-----------------|-----------------|-----------------|
|                 | Lactate Period  | Bicarbonate Period |
|                 | Baseline        | 3 mo             | Baseline        | 3 mo             |
| **Blood pH**    | 7.4 ± 0.06      | 7.38 ± 0.05      | 7.4 ± 0.05      | 7.43 ± 0.06a     |
| **Blood bicarbonate level (mM)** | 23.7 ± 5.3      | 22.8 ± 3.9       | 22.7 ± 4.3      | 24.6 ± 2.3ab     |
| **Base excess (mM)** | −0.5 ± 5.4      | −1.5 ± 4.1       | −1.5 ± 4.7      | 0.7 ± 2.8ab      |
| **Blood CO₂ pressure (mmHg)**  | 38.5 ± 6.3      | 39.4 ± 5         | 36.4 ± 6.6      | 38.1 ± 4.8       |
| **Serum lactate level (mM)**   | 1.51 ± 0.76     | 1.45 ± 1.15      | 1.52 ± 0.48     | 1.47 ± 0.53      |

a P < 0.05, for intraindividual comparison versus end of lactate period for patients who completed both study periods (n = 16) (signed rank or t test, as appropriate).

b P < 0.05, for intraindividual comparison versus baseline.
lactate fluid, during which any oral bicarbonate supplementation started during the first study period was discontinued.

During the study, all patients maintained their previous APD prescriptions, which were adapted according to clinical needs and accepted adequacy targets (20). Bicarbonate medication was reintroduced only when blood bicarbonate levels were <18 mM at two consecutive visits.

Every 4 wk, a physical examination (including total body water assessment by bioimpedance analysis in one center) (21) and a laboratory evaluation were performed. Blood gas analyses were performed with arterialized capillary blood samples. At the start of the study and at the end of each 12-wk period, a standardized peritoneal equilibration test (PET) (using a fill volume of 1000 ml/m² body surface area and 2.4% glucose, according to standardized pediatric procedural guidelines) (22), dialytic and urinary 24-h clearance studies, assessments of dialysate albumin, β₂-microglobulin, carcinoembryonic antigen-125 (CA125), TGF-β, and VEGF levels, and differential cell counts of the 4-h effluent were also performed (23).

Episodes of peritonitis during the trial were diagnosed and treated according to a standardized protocol that had been previously established by the Mid European Pediatric Peritoneal Dialysis Study Group consortium (24). For patients for whom an episode of peritonitis occurred during the final 1 mo of a treatment period (lactate, n = 1; bicarbonate, n = 2), treatment was extended and the post-treatment PET was postponed by 4 wk, to exclude the possibility of interference from inflammation-related effects. None of the acid-base status, peritoneal transport, or clearance characteristics and no dialysate marker concentrations differed significantly between patients with or without peritonitis, in either treatment group.

**Laboratory Analyses**

Blood pH, carbon dioxide pressure, and oxygen pressure were measured immediately with a blood gas analyzer, and actual bicarbonate concentrations were calculated by using the Henderson-Hasselbalch equation. The blood and dialysate concentrations of glucose, creatinine, urea, lactate, electrolytes, inorganic phosphate, albumin, and β₂-microglobulin and the serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, total protein, triglyceride, cholesterol, and C-reactive protein were measured centrally at the Heidelberg University Medical Center laboratory, with standard analytical methods. Effluent CA125 concentrations were measured with an electrochemiluminescence immunosay (Roche Diagnostics GmbH, Mannheim, Germany), and TGF-β1 and VEGF levels were measured with ELISA (R&D Systems GmbH, Wiesbaden, Germany). Dialysate creatinine measurements were corrected for the presence of glucose, as described previously (23).

**Statistical Analyses**

Paired t tests were used to assess intraindividual changes among patients who completed individual 3-mo periods, i.e., lactate (at baseline) followed by lactate, lactate (at baseline or the end of the first study period) followed by bicarbonate, and bicarbonate followed by lactate dialysis. Changes in acid-base status and biochemical parameters measured at 4-wk intervals were assessed with bivariate, repeated-measures ANOVA for time- and treatment-related effects, using the Contrast option in the Repeated statement of the general linear model procedure in SAS software (SAS, Cary, NC) to identify individual time points with significant deviations from baseline values. Stepwise linear regression analysis was used to identify independent predictors of changes in blood pH during the lactate and bicarbonate PD periods. Data are presented as mean ± SD.

**Results**

**Acid-Base Status, Serum Biochemical Findings, and Body Composition**

Nine of 28 patients were receiving oral bicarbonate therapy at the time of recruitment. The discontinuation of oral bicarbonate therapy 2 wk before randomization resulted in moderate metabolic acidosis (blood pH of <7.35) for 21% of the patients. Among the patients who completed at least one study period (bicarbonate, n = 20; lactate, n = 20), blood pH and blood bicarbonate concentrations gradually increased with bicarbonate but slightly decreased further with lactate solution, resulting in significant differences in the acid-base status after 3 mo (Table 1 and Figure 1). For patients who switched from bicarbonate to lactate dialysis according to the randomization scheme, significant decreases in blood pH (from 7.43 ± 0.04 to 7.38 ± 0.05, P < 0.05) and blood bicarbonate levels (from 25 ± 1.5 mM to 22.9 ± 3.4 mM, P = 0.05) occurred within 3 mo. Blood carbon dioxide pressure and serum lactate concentrations remained unchanged in the two treatment periods (Table 1). Oral bicarbonate supplementation was reintroduced during two of 20 bicarbonate and four of 20 lactate dialysis periods and did not differ quantitatively between the treatment groups.

During both treatment periods, the change in blood pH was inversely correlated with the pH value at the beginning of the period (lactate, r = −0.68, P < 0.01; bicarbonate, r = −0.70, P < 0.01), i.e., blood pH tended to decrease among alkalotic patients and to increase among acidotic patients. In the bicarbonate but not the lactate treatment period, the pH change was also inversely correlated with the age of the patients (r = −0.54, P < 0.05) (Figure 2). Stepwise linear regression analyses revealed that the initial pH (partial R² = 0.49, P < 0.005) and patient age (partial R² = 0.29, P < 0.001) were indepen-

**Figure 1.** Blood pH (left) and changes in blood bicarbonate levels (right) among children undergoing automated peritoneal dialysis (APD) who received 34 mM bicarbonate (open circles) or 35 mM lactate (closed squares) peritoneal dialysis (PD) solution for 3 mo. Each curve represents 20 complete treatment periods; 16 patients completed both lactate and bicarbonate treatment phases. *P < 0.05, significant intraindividual differences.
CA125 concentrations remained unchanged among patients who underwent continued lactate dialysis (Figure 3). Effluent CA125 concentrations were inversely correlated with dialysate volume ($r = -0.54$, $P < 0.05$) and dialytic glucose exposure ($r = -0.60$, $P < 0.01$) with lactate PD fluid but not bicarbonate fluid. The 4-h effluent concentrations of VEGF and TGF-β1 did not change consistently with either PD fluid (VEGF, 24.6 ± 13.3 pg/ml at the beginning and 36.2 ± 19.8 pg/ml at the end of the lactate period, 30.7 ± 24.1 pg/ml at the beginning and 33.9 ± 26.7 pg/ml at the end of the bicarbonate period; TGF-β1, 57.4 ± 46.4 pg/ml at the beginning and 61.1 ± 22.9 pg/ml at the end of the lactate PD period and 60.1 ± 44.2 pg/ml at the beginning and 56.3 ± 30.9 pg/ml at the end of the bicarbonate period).

**Efficacy of Dialysis**

The dialysis dose, i.e., fluid turnover and cumulative glucose exposure, remained unchanged during the two study periods (Table 2). Daily ultrafiltration rates at the end of each period did not differ, either in absolute terms or with normalization to glucose exposure. The use of bicarbonate PD fluid was associated with subtle changes in peritoneal transport characteristics (Table 2). Creatinine equilibration was slightly reduced, resulting in lower 1-h and 4-h dialysate/plasma ratios at the end of the bicarbonate study period, compared with the PET performed after the lactate period ($P < 0.05$). This difference in solute transport caused a significant reduction in the PET 4-h creatinine clearance after bicarbonate dialysis (5.3 ± 1.3 ml/min per 1.73 m²), compared with the PET 4-h creatinine clearance at the end of the lactate PD period (5.7 ± 1.1 ml/min per 1.73 m², $P < 0.05$).

**Adverse Events**

Six episodes of peritonitis were observed in 63 patient-mo of bicarbonate fluid treatment and 10 episodes were observed in 109 patient-mo of lactate fluid treatment (including run-in and washout periods; $P = NS$). Episodes of relapsing peritonitis (as previously defined) (24) were observed for three patients receiving bicarbonate and two patients receiving lactate PD fluid. Other reported adverse events were episodes of acute fluid overload (total body water of >70%; bicarbonate, 1.5 episodes/12 patient-mo; lactate, 1.8 episodes/12 patient-mo; $P = NS$), aggravated hypertension (BP >10% above 95th percentile value; bicarbonate, 1.6 episodes/12 patient-mo; lactate, 2.2 episodes/12 patient-mo; $P = NS$), and severe hyperparathyroidism (parathyroid hormone levels of >500 pg/ml; bicarbonate, 1.0 episode/12 patient-mo; lactate, 0.9 episode/12 patient-mo; $P = NS$).

**Discussion**

In this randomized prospective trial, superior correction of metabolic acidosis was achieved with administration of a neutral-pH, purely bicarbonate-buffered dialysis fluid among children undergoing APD. Moreover, indirect evidence suggests that chronic application of the bicarbonate PD solution is associated with an increase in mesothelial cell mass, indicating improved in vivo biocompatibility of this new fluid.

Conventional PD fluids contain 35 mM lactate buffer at
Table 2. Peritoneal dialysis dose and peritoneal transport characteristics at baseline and after 12 wk of lactate (n = 20) or bicarbonate (n = 20) dialysis

<table>
<thead>
<tr>
<th></th>
<th>Lactate Period</th>
<th>Bicarbonate Period</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 mo</td>
</tr>
<tr>
<td>Dialysate turnover (L/m² per 24 h)</td>
<td>8 ± 2.9</td>
<td>8 ± 3.4</td>
</tr>
<tr>
<td>Peritoneal glucose exposure (g/m² per 24 h)</td>
<td>156 ± 65</td>
<td>154 ± 75</td>
</tr>
<tr>
<td>Dialytic creatinine clearance (L/wk per 1.73 m²)</td>
<td>42.1 ± 11.5</td>
<td>41.3 ± 16.3</td>
</tr>
<tr>
<td>Dialytic Kt/Vurea (L/wk per 1.73 m²)</td>
<td>2.50 ± 0.83</td>
<td>2.32 ± 0.83</td>
</tr>
<tr>
<td>Residual GFR (ml/min per 1.73 m²)</td>
<td>2.2 ± 1.8</td>
<td>2.3 ± 1.7</td>
</tr>
<tr>
<td>24-h ultrafiltration (ml/m²)</td>
<td>615 ± 550</td>
<td>468 ± 802</td>
</tr>
<tr>
<td>1-h D/P creatinine</td>
<td>0.41 ± 0.08</td>
<td>0.42 ± 0.11</td>
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<tr>
<td>4-h D/P creatinine</td>
<td>0.72 ± 0.1</td>
<td>0.76 ± 0.14</td>
</tr>
<tr>
<td>1-h D/D₀ glucose</td>
<td>0.56 ± 0.1</td>
<td>0.57 ± 0.1</td>
</tr>
<tr>
<td>4-h D/D₀ glucose</td>
<td>0.28 ± 0.06</td>
<td>0.27 ± 0.1</td>
</tr>
<tr>
<td>4-h D/P β₂-microglobulin</td>
<td>0.12 ± 0.05</td>
<td>0.12 ± 0.05</td>
</tr>
<tr>
<td>4-h D/P albumin</td>
<td>0.016 ± 0.016</td>
<td>0.014 ± 0.004</td>
</tr>
<tr>
<td>4-h ultrafiltration (ml/m²)</td>
<td>133 ± 228</td>
<td>113 ± 204</td>
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* D/P, dialysate/plasma ratio; D/D₀, dialysate/beginning dialysate ratio.
³ p < 0.05, for intraindividual comparison versus end of lactate period for patients who completed both study periods (n = 16).

acidic pH (pH 5.5). Lactate is rapidly absorbed and converted to bicarbonate in the liver, and bicarbonate is lost into the dialysate (9,15). Correction of acidosis is achieved with the net absorption of base equivalents, resulting from the reciprocal movements of lactate and bicarbonate. In contrast, with pure bicarbonate solutions, correction of metabolic acidosis occurs with unidirectional bicarbonate absorption. Here we present the first extended application among APD patients of a PD solution containing pure 34 mM bicarbonate. Metabolic acidosis was corrected more efficiently with this fluid than with a standard PD fluid containing 35 mM lactate buffer. The differences in acid-base status gradually increased with time and became significant after 3 mo of administration.

The superior buffering efficacy of the bicarbonate solution, which was reproducible and fully reversible in the crossover application, was an unexpected finding. In a recent pharmacokinetic comparison, we did not observe differences in net base flux between 34 mM bicarbonate and 35 mM lactate PD fluids during a 4-h PET or a single day of APD (9). This finding does not exclude the possibility of subtle differences in the early transport kinetics of bicarbonate and lactate, which could accumulate with time during continued APD with frequent short cycles.

Analysis of potential predictors of the blood pH response revealed an inverse relationship between pH changes and patient age during bicarbonate but not lactate dialysis. The effect was not accounted for by age-related differences in baseline blood pH, the delivered dialysis dose, peritoneal transport characteristics, or residual renal function. A possible explanation might involve the age-related increase in the carbonate pool of the growing skeleton. More than 50% of total body carbon dioxide is stored as carbonate complexes in bone (25). Animal studies have demonstrated that the infantile skeleton contains a relatively smaller carbonate compartment, which is compensated for by a larger phosphate compartment to buffer protons in metabolic acidosis (26). Sustained peritoneal bicarbonate absorption may replete the bone carbonate stores more rapidly among young children, resulting in more efficient correction of metabolic acidosis.

It remains to be determined why the inverse relationship between age and blood pH changes was limited to bicarbonate PD fluid and was not observed with lactate fluid. We speculate that this difference might be explained by developmental differences in acid-base metabolism. The conversion of absorbed lactate to bicarbonate critically depends on liver function and was inefficient among patients with impaired hepatic function resulting from septic shock (27). Inefficient hepatic conversion of lactate to bicarbonate, with subsequent lactic acidosis, was also reported for neonates receiving lactate-buffered PD fluid and was attributed to the physiologic immaturity of the liver (14). The time course of the postnatal maturation of lactate metabolism has not been delineated; it is possible that the liver achieves full lactate-degrading capacity only several years after birth. However, serum lactate concentrations did not differ between the lactate and bicarbonate treatment periods or between infants and older children.

The superior correction of metabolic acidosis with bicarbonate PD fluid among children is of immediate clinical relevance. With conventional lactate-based solutions, approximately 30% of children undergoing chronic PD require additional oral sodium bicarbonate supplementation, indicating inefficient correction of metabolic acidosis with lactate buffer (2). Metabolic acidosis is a particularly detrimental complication of renal failure among children, because of its adverse effects on bone mineralization, nutritional status, and body growth (28,29). Moreover, the need for oral administration of large
amounts of sodium bicarbonate is a major burden for many patients and families. More efficient acidosis correction with bicarbonate PD fluid may reduce the morbidity and stress resulting from this complication, particularly among infants.

This study also investigated whether a neutral-pH, pure bicarbonate solution with a very low glucose degradation product content would exhibit improved peritoneal biocompatibility among pediatric APD patients. The dialysis effluent concentration of CA125 (a glycoprotein that is constitutively expressed by vital mesothelial cells) was used as a bulk marker of the mesothelial cell layer (30,31). We indeed observed an increase in peritoneal CA125 outflow of 100% during bicarbonate dialysis, which was fully reversible with a return to the conventional lactate solution. This result is in accordance with recent observations among adult patients undergoing continuous APD who were treated with several new PD solutions produced with dual-compartment technology (16–19). Because those biocompatible solutions contained either lactate (16–18) or a lactate/bicarbonate mixture (19) and were buffered at either neutral pH (16,19) or mildly acidic pH (17,18), it is likely that the marked reduction in glucose degradation product contents that is common to all new PD solutions is the major factor contributing to their improved biocompatibility. Interestingly, we noted an inverse relationship between effluent CA125 concentrations and total dialytic glucose exposure when lactate but not bicarbonate solution was used. Because the glucose degradation product contents of conventional PD fluids are proportional to their glucose contents, this observation supports the idea that glucose degradation products, rather than glucose itself, may causally contribute to the mesothelial cell toxicity of conventional solutions. The readily reversible response of peritoneal CA125 release to changing exposures to conventional or biocompatible PD fluids is remarkable and deserves further evaluation. The precise time course of the effect, additional markers of cell function, and, ultimately, histopathologic specimens must be investigated to determine whether the increased CA125 release with the new fluids reflects functional recovery of the existing cell layer or a net increase in cell mass attributable to reduced cell death and/or proliferation of mesothelial cells in situ (8).

Moreover, extended studies are required to ascertain whether use of the new PD solutions would slow the process of neoangiogenesis and submesothelial fibrosis, leading to ultrafiltration failure among patients undergoing long-term PD. We did not observe any effects on peritoneal VEGF or TGF-β release, but the validity of these growth factors as markers of local neoangiogenic and fibrotic activity is not established and the follow-up period might have been too short for detection of treatment-related effects.

Finally, the analysis of pre- and post-treatment peritoneal solute transport rates revealed a slowing of creatinine equilibration after bicarbonate APD of approximately 10%. This slight but significant difference yielded a similar decrease in the dialytic creatinine clearance measured during the PET. These results are in quantitative agreement with the slight reduction in creatinine transport observed in a previous comparison of the immediate pharmacokinetic effects of the two solutions, when administered on sequential days (9). The observed effects may be attributable to less marked initial vaso-dilation of resistance arterioles and/or recruitment of peritoneal capillaries by the neutral-pH bicarbonate solution, resulting in a slightly smaller functional peritoneal surface area in the early phase of the dialysis cycle (32,33). It is tempting to speculate that a more marked reduction of the functional peritoneal surface area attributable to reduced hyperperfusion might have been prevented by the increased release of CA125 by mesothelial cells, which might increase the peritoneal surface area available for solute exchange by virtue of its strong lubricating properties (34).

Although the factors responsible for less marked initial peritoneal hyperperfusion with the bicarbonate solution may prove beneficial for long-term preservation of the peritoneal membrane, it is conceivable that lower permeability may also result in reductions in small-solute elimination rates and a lower delivered dialysis dose, particularly among APD patients with short dwell times. However, the clearance changes observed in this study were quantitatively insignificant and could easily be compensated for by slightly increasing the prescribed dialysis dose.

In conclusion, this clinical trial revealed clinically relevant benefits of a bicarbonate-based, neutral-pH PD solution among children undergoing APD. Whereas the apparently improved peritoneal biocompatibility should be equivalent to that reported for other new PD solutions, the 34 mM pure bicarbonate buffer content seemed to provide superior correction of acidosis, compared with lactate-buffered fluids, especially among young children.

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References