PART FOUR

Metabolism and Nutrition
Metabolic acidosis correction is one of the goals of renal replacement therapy. Correction of acidosis in peritoneal dialysis (PD) may be affected by PD modalities such as automated PD (APD) or by new solutions containing a combination of bicarbonate and lactate as a buffer [bicarbonate continuous ambulatory PD (CAPD)]. The aim of the present study was to examine the acid–base status of our PD population and to compare the effects of APD, lactate CAPD, and bicarbonate CAPD on serum bicarbonate levels.

We studied 35 stable patients undergoing APD (n = 15), lactate-buffered (35 mEq/L) CAPD (n = 14), and bicarbonate/lactate–buffered CAPD (n = 6) for 48.5 ± 38.1 months.

Most of our patients had serum bicarbonate levels in the normal range. In 3 patients (8%), HCO₃ was below 22 mEq/L, and in 8 patients (22%; APD = 2, lactate CAPD = 2, bicarbonate CAPD = 4), HCO₃ was above 28 mEq/L. We found no statistically significant correlations between HCO₃ serum levels and PD prescription, peritoneal membrane characteristics, or intake of calcium carbonate and sevelamer hydrochloride. Patients on bicarbonate CAPD had higher HCO₃ serum levels, but this difference disappeared when corrections for duration of dialysis, residual urine volume, and PD adequacy indices were applied.

In the studied PD population, adequate correction of metabolic acidosis was achieved, as reflected in serum bicarbonate levels. We observed no difference in serum bicarbonate levels between APD and lactate CAPD patients. The new bicarbonate-buffered PD solutions are more biocompatible and can result in higher serum bicarbonate levels. However, a significant number of PD patients on bicarbonate-buffered solutions may become alkalotic. The clinical significance of these results needs further examination in prospective studies.

Key words
Metabolic acidosis, bicarbonate solution, lactate solution

Introduction
Chronic metabolic acidosis is commonly observed in patients with chronic renal insufficiency, because the kidney is the organ normally responsible for generating alkali to maintain acid–base homeostasis (1). Replacement of renal function by hemodialysis (HD) or peritoneal dialysis (PD) can restore serum bicarbonate levels or even normalize them in some patients (2).

Since the introduction of PD, lactate buffering has been used without any major clinical adverse effects, but since the mid-1990s, several investigators have noted that the use of the standard lactate concentration (35 mEq/L) presents some problems, such as biocompatibility, metabolic side effects, and lack of full correction of acidosis (2,3). Correction of acidosis was markedly improved with the use of a new lactate-containing solution (40 mEq/L), but a substantial number of patients remained acidic and an increased number of patients developed metabolic alkalosis (2).
The introduction of automated PD (APD), with the wide use of cyclers, offered some new advantages regarding solute clearance and perhaps reduced peritonitis rates, but only a few studies have examined the role of cyclers in the correction of metabolic acidosis (4).

In recent years, lactate-free and low-lactate solutions—those containing only bicarbonate or a mixture of bicarbonate and lactate as a buffer—have been studied and approved for use in PD patients (5–8). The aim of the present cohort study was to examine the acid–base status of our PD population and to compare the effects of APD, lactate-buffered CAPD (lactate CAPD), and bicarbonate/lactate–buffered CAPD (bicarbonate CAPD) on acid–base homeostasis.

Patients and methods

Patients who had been undergoing PD by any modality for more than 3 months in our center were eligible for the study. We enrolled 35 stable patients (17 men, 18 women) undergoing APD (n = 15), lactate CAPD (n = 14), and bicarbonate CAPD (n = 6). Table I shows the characteristics for the patients overall and for the subgroups.

Patients undergoing lactate CAPD used a regimen of 4 exchanges per day, in a twin-bag system with a solution containing 35 mEql/L lactate (Dianeal PD1: Baxter Healthcare SA, Castlebar, Ireland; or Stay•Safe CAPD: Fresenius Medical Care, Bad Homburg, Germany).

Patients undergoing APD used a regimen of 8–12 hours of overnight PD by cycler (HomeChoice: Baxter Healthcare; or Sleep•Safe: Fresenius Medical Care) with a total of 12–20 L of lactate-buffered solution, with or without a daytime exchange. The patients were selected for APD for social reasons, because of their peritoneal membrane characteristics (they were high transporters on a standard peritoneal equilibration test), or because of transfer from CAPD as a consequence of low clearances (underdialysis).

The 6 patients undergoing bicarbonate CAPD used a bicarbonate/lactate–buffered solution (25 mmol/L and 15 mmol/L respectively; Physioneal: Baxter Healthcare).

Plasma bicarbonate levels were measured in venous blood, sampled without stasis, by a blood gas analyzer. Blood was taken into a heparinized syringe and immediately transported to the analyzer for analysis. Actual plasma bicarbonate was calculated by the analyzer from pH and pCO₂ according to the Henderson–Hasselbach formula. The analyzer also calculated anion gap by the formula

\[ \text{Na} – (\text{HCO}_3^- + \text{Cl}^-). \]

Patients were considered to be acidicotic if their venous bicarbonate level was below 22 mEq/L and alkalotic if the level was above 28 mEq/L.

We assessed peritoneal membrane characteristics and urea and creatinine urinary and peritoneal clearances for each patient by standard peritoneal equilibration test and 24-hour spent dialysate collection 2 months before and after bicarbonate sampling. Body mass index (BMI) was calculated from height (m²) and weight (kg) measurements for each patient.

<table>
<thead>
<tr>
<th>TABLE I Patient characteristics</th>
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</thead>
<tbody>
<tr>
<td><strong>APD</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Men/women</td>
</tr>
<tr>
<td>PD duration (months)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Renal diseases</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>APKD</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Unknown causes</td>
</tr>
</tbody>
</table>

APD = automated peritoneal dialysis; L-CAPD = continuous ambulatory peritoneal dialysis with lactate-buffered solution; BL-CAPD = continuous ambulatory peritoneal dialysis with bicarbonate/lactate–buffered solution; BMI = body mass index; APKD = adult polycystic kidney disease.
No patient was receiving furosemide or any other diuretic, because our policy is to withdraw diuretics after the commencement of renal replacement therapy. In addition, for every patient, we recorded the phosphate binder medications (class and dosing) used during the month of the study. No patient received sodium bicarbonate orally.

All statistics are expressed as mean ± standard deviation. Correlations between serum HCO$_3$ and anion gap and various parameters were studied by linear regression analysis. Differences between the groups were analyzed by $t$-test for independent samples. Values of $p$ below 0.05 were considered statistically significant.

**Results**

The mean serum bicarbonate level of the patients was 25.2 ± 3.2 mEq/L. Most patients had a serum bicarbonate level in the normal range. In 3 patients (8%; APD = 2, lactate CAPD = 1), HCO$_3$ was less than 22 mEq/L, and in 8 patients (22%; APD = 2, lactate CAPD = 2, bicarbonate CAPD = 4), HCO$_3$ was above 28 mEq/L. Table II shows the full data for HCO$_3$, pH, anion gap, Kt/V urea, creatinine clearance, urinal volume, urinary creatinine clearance, 4-hour dialysate-to-plasma (D/P) creatinine, and final-to-initial ratio of dialysate (D/D$_0$) glucose. No statistically significant correlations could be detected between anion gap or HCO$_3$ serum level and duration of PD, BMI, D/P creatinine, D/D$_0$, Kt/V urea, creatinine clearance, residual urine volume, or urinary creatinine clearance.

We observed no differences between APD and lactate CAPD patients. Bicarbonate CAPD patients had higher serum levels of HCO$_3$ than did APD and lactate CAPD patients ($p < 0.05$). However, the bicarbonate CAPD patients had significantly larger residual urine volumes than did the patients on APD ($p < 0.01$) and on lactate CAPD ($p < 0.05$). Urinary creatinine clearance was also higher in the bicarbonate CAPD group than in the APD group ($p < 0.05$).

In regard to phosphate binders, 15 patients were receiving sevelamer hydrochloride (APD = 10, lactate CAPD = 4, bicarbonate CAPD = 1), 10 were receiving calcium carbonate (APD = 3, lactate CAPD = 5, bicarbonate CAPD = 2), 3 patients were receiving both binders (1 patient in each group), 4 patients were receiving no binders, and 3 patients were receiving aluminum hydroxide (lactate CAPD = 2, bicarbonate CAPD = 1) during the study period. The doses of sevelamer ranged from 2 to 12 tablets (800 mg each) and of calcium carbonate from 6 to 16 tablets (500 mg each). No effect of the phosphate binders on serum HCO$_3$ and pH could be detected.

**Discussion**

Metabolic acidosis is a major metabolic abnormality in end-stage renal disease, and alkali is provided with dialysis treatment to keep acid–base balance within a normal range (1). The ongoing changes in PD technology, such as new delivery modes (cyclers) (4) and new buffers (bicarbonate and bicarbonate/lactate) (5–8) require a re-examination of acid–base status in patients undergoing PD.

**TABLE II** Laboratory and dialysis parameters in the full study population and in the groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APD</th>
<th>L-CAPD</th>
<th>BL-CAPD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCO$_3$ (mmol/L)</td>
<td>24.3±3.2</td>
<td>26±3.1</td>
<td>28.5±2.5</td>
<td>25.2±3.2</td>
</tr>
<tr>
<td>Anion gap (mEq/L)</td>
<td>13.8±2.1</td>
<td>12.37±4.1</td>
<td>13±1.7</td>
<td>13.2±2.8</td>
</tr>
<tr>
<td>Kt/V urea</td>
<td>2.05±0.3</td>
<td>1.93±0.4</td>
<td>2.22±0.2</td>
<td>1.98±0.4</td>
</tr>
<tr>
<td>Weekly CCr (mL/min)</td>
<td>72.8±27.3</td>
<td>81.6±38</td>
<td>92.9±31.2</td>
<td>77.8±33.5</td>
</tr>
<tr>
<td>Weekly urinary CCr (mL/min)</td>
<td>14.8±29.9</td>
<td>24.26±42.1</td>
<td>48.3±40.1</td>
<td>24.35±37.6</td>
</tr>
<tr>
<td>D/P creatinine</td>
<td>0.73±0.07</td>
<td>0.67±0.11</td>
<td>0.67±0.13</td>
<td>0.70±0.1</td>
</tr>
<tr>
<td>D/D$_0$ glucose</td>
<td>0.31±0.05</td>
<td>0.34±0.07</td>
<td>0.35±0.08</td>
<td>0.33±0.06</td>
</tr>
<tr>
<td>Urine volume (mL/24 h)</td>
<td>200±352</td>
<td>698±964</td>
<td>1333±1290</td>
<td>478±789</td>
</tr>
</tbody>
</table>

$^a$ Significantly different from APD ($p < 0.05$) and L-CAPD ($p < 0.05$).

$^b$ Significantly different from APD ($p < 0.05$).

$^c$ Significantly different from APD ($p < 0.01$) and L-CAPD ($p < 0.05$).

APD = automated peritoneal dialysis; L-CAPD = continuous ambulatory peritoneal dialysis with lactate-buffered solution; BL-CAPD = continuous ambulatory peritoneal dialysis with bicarbonate/lactate–buffered solution; Kt/V urea = dialysis adequacy; CCr = creatinine clearance; D/P = dialysate-to-plasma ratio; D/D$_0$ = final-to-initial ratio of dialysate glucose.
The introduction of the new bicarbonate and bicarbonate/lactate solutions has been a major breakthrough in the recent years for biocompatibility, because they also have low glucose degradation products (5,7,8). Initial studies indicated that they may also provide better acid–base control, which is, without doubt, favorable for pediatric patients (6). However, the issue of partial or full correction of metabolic acidosis in HD and PD adult patients remains a matter of debate. Low serum bicarbonate levels (<19 mEq/L) are associated with increased mortality, but optimal levels remain to be defined (1). Metabolic alkalosis may be deleterious in theory by promoting vascular calcifications (1,3). We have observed that most of our patients on bicarbonate CAPD present high bicarbonate levels, and the issue remains open for further study.

In the present study, we investigated the acid–base profile of our PD population, which consisted of patients undergoing APD, lactate CAPD, and bicarbonate CAPD. Patients on APD and lactate CAPD presented equivalent acid–base profiles; patients on bicarbonate CAPD had higher serum bicarbonate levels—often in the range of alkalosis (>28 mEq/L). Mean serum bicarbonate levels in venous blood samples in our study were 25.2 ± 3.2 mEq/L. These results accord with other studies of bicarbonate levels in PD patients. Kung et al. (9) reported mean HCO₃ levels of 25.9 mEq/L; Dumler and Galan (10), levels of 25 ± 4 mEq/L; Mujais (4), 25.3 ± 0.24 mEq/L in CAPD patients and 25.73 ± 0.36 mEq/L in APD patients; and Kasimatis et al. (11), 26 ± 2.4 mmol/L. On the other hand, Tian et al. reported a high incidence of metabolic acidosis (43%) in a Chinese PD population (12).

We found no significant correlation between serum HCO₃ level or anion gap and any of the other parameters studied. In CAPD patients, Mujais reported that low HCO₃ levels were inversely correlated with blood urea nitrogen (BUN) and albumin and phosphate levels, and positively correlated with 4-hour D/P creatinine. In APD patients, the same author reported an inverse correlation of HCO₃ with BUN and phosphate (4). But these correlations were rather weak. The small number of patients in our study may have been the reason that we observed no significant correlations, as did Mujais in his study (4).

Kasimatis et al. (11) reported that, in a multivariate analysis, HCO₃ levels were directly correlated with older age and use of CaCO₃ as a phosphate binder, and inversely associated with serum potassium and the use of sevelamer and of low-lactate dialysis solutions. Higher serum urea levels, the use of low-lactate solutions, and use of sevelamer instead of CaCO₃ were significantly predictive of HCO₃ levels below 24 mmol/L.

In our study population, 8% of the PD patients presented HCO₃ levels below 22 mmol/L. Mujais reported a similar percentage (10%) in his APD and lactate-buffered CAPD populations, although data about the concentration of lactate used in the PD solution in that study (35 or 40 mmol/L) are missing (4). Kasimatis et al. (11) reported that 13.5% of their PD population had HCO₃ levels below 24 mmol/L. We found an incidence of 22% of high bicarbonate levels mainly in patients undergoing CAPD with the new bicarbonate/lactate solution. Interestingly, Mujais (4) reported a similar percentage (17%–27%) in his study, which did not use these new solutions.

In our study, the mean anion gap was 13.2 ± 2.8 mEq/L—almost the same as those of Kasimatis et al. (11), who found an anion gap of 13.1 ± 3.1 mEq/L, and Tian et al. (12). Mujais (4) reported a higher anion gap (21.2 ± 0.3), but the calculations in his study clearly used potassium levels to make the estimation. Still, even after correction for potassium, the levels in the Mujais study remained higher than those in our study or in other studies (11,12).

Otherwise, our results accord with those of Mujais and show equal correction of metabolic acidosis in patients undergoing APD and lactate CAPD. The use of short cycles in APD might be expected to alter the kinetics of buffer exchange, but the net overall effect on correction of acidosis appears to be identical. In addition, in neither group did the level of residual renal function influence bicarbonate levels, indicating that the provision of alkali via these modalities can override the impact of residual renal function. Notably, Tian et al. (12) recently reported that CAPD patients with better residual renal function were more susceptible to normal anion metabolic acidosis and that the renal loss of bicarbonate may, to a large extent, be responsible for the occurrence of acidosis in these patients. These results have not been confirmed by other studies.

Finally, with regard to phosphate binders, we were unable to detect any significant effect of calcium carbonate or sevelamer hydrochloride on acid–base
Acid-Base Profile in PD

profile in PD patients. Calcium carbonate is well known to be useful as a buffer for patients with chronic kidney disease stages 3 and 4. Sevelamer hydrochloride has been implicated in a deterioration of metabolic acidosis in HD patients and has not received official approval for use in pre-dialysis patients (13). Kasimatis et al. (11) reported that use of sevelamer may be a factor in reduced HCO₃⁻ levels in PD patients. Although more than 50% of our patients received sevelamer alone or in combination with calcium carbonate, we could find no effect on acid–base status. Perhaps increased dialysis dosing and the new PD solutions are able to overcome the acid load of sevelamer.

Our study is unique in that our policy calls for diuretics to be stopped as soon as our patients start renal replacement therapy (HD or PD). In addition, a significant number of our patients maintain well-preserved residual renal function for a long time. Almost all of the studies in the literature note the use of high-dose diuretics for patients with significant residual renal function, and these medications are well known to have an impact on acid–base profile. Perhaps, if we also used diuretics, we would also see higher serum HCO₃⁻ levels.

One of the main goals of our program is to achieve the highest level of PD clearance possible. To reach this goal, we measure dialysis dose frequently and do not hesitate to use high-dose APD (15 – 20 L daily) when adequacy targets cannot be achieved. This policy achieves rather high Kt/V urea clearances even in anuric patients, and this situation may perhaps explain the correction of metabolic acidosis with standard low-lactate PD solutions.

Conclusions

Our PD population presents adequate correction of metabolic acidosis as reflected in their serum bicarbonate levels. This correction might be attributed to frequent adjustments of dialysis dose to achieve optimum targets for PD adequacy. When adequacy targets are met, lactate-based PD solutions may provide adequate serum HCO₃⁻ correction for APD and CAPD patients alike. The new bicarbonate-buffered PD solutions are more biocompatible and can result in higher serum bicarbonate levels. However, a significant number of PD patients on bicarbonate-buffered solutions may become alkalotic. The clinical significance of alkalosis needs further examination in prospective studies.

References


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