Correcting Acidosis in Hemodialysis: Effect on Phosphate Clearance and Calcification Risk

David C.H. Harris, Elisabeth Yuill, and Douglas W. Chesher

ABSTRACT

Control of uremic acidosis by hemodialysis carries the potential risks of reducing phosphate clearance and worsening metastatic calcification; modeling bicarbonate delivery has been proposed to adequately correct acidosis without impairing phosphate removal. To test the efficacy and safety of different methods for controlling acidosis, nine stable adults received in random order standard (S; dialysate HCO$_3^-$ 30 to 34 mmol/L), high (H; 40 mmol/L) or modeled (M; 28 mmol/L, rising exponentially to 35 mmol/L at 3 h, 40 mmol/L at 4 h) bicarbonate dialysis for 4 wk each, and were tested during the last two dialyses of each treatment. More oral bicarbonate capsules were required with M than H (2.8 ± 0.4 versus 1.4 ± 0.4/day, P = 0.04) to maintain predialysis HCO$_3^-$ at 24 to 26 mmol/L. Plasma HCO$_3^-$ was significantly higher with H than M during dialysis, and than S before, during, and after dialysis. Plasma inorganic phosphate, phosphate rebound, clearance of phosphate from plasma (80 to 90 mL/min) and mass transfer of phosphate into dialysate (12 to 13 mmol/4 h dialysis) were no different among the three treatments. Similarly, there were no differences in plasma concentration of urea, total calcium, estimated ionized calcium, lipids, and potassium, clearance and mass transfer of urea, blood pressure, and symptoms with the three treatments. Estimated levels of tribasic inorganic phosphate, the phosphate component of hydroxyapatite, were very similar before and after each treatment. Plasma calcium × phosphate product was less than 3.5 mmol$^2$/L$^2$ at all times with each treatment. A risk factor for metastatic calcification was calculated from the relative saturation ratio of its principle component, hydroxyapatite (Ca$_5$ (PO$_4$)$_3$ OH); this was no different among each of the treatments, and was not altered significantly by dialysis. Uremic acidosis can be fully corrected by high or modeled bicarbonate dialysis without any reduction of phosphate clearance or increased risk of metastatic calcification. The added cost of modeling technology is not justified by the criterion of phosphate clearance alone.

Key Words: Bicarbonate, phosphate, modeling, dialysis, metastatic calcification

Hyperphosphatemia and acidosis are two metabolic consequences of renal failure that are often poorly controlled in dialysis patients. Inadequately controlled metabolic acidosis contributes to renal osteodystrophy and malnutrition, and hyperphosphatemia results in secondary hyperparathyroidism and metastatic calcification; together they account for a sizable proportion of the morbidity of renal failure. Dialytic removal of phosphate is limited by its mobilization from a deep pool into extracellular fluid during the dialysis procedure. Alkalosis may increase the shift of phosphate into erythrocytes, and thus reduce its availability for removal by dialysis. In contrast, acidosis may increase intracellular generation of phosphate. Intracellular shift of phosphate may also be increased by the dialysate buffer base acetate, even when used in low concentration. Thus, there is some evidence, albeit conflicting, that bicarbonate dialysis may result in greater phosphate clearance than acetate dialysis. Rebound hyperphosphatemia, a postdialysis consequence of continued release of phosphate into extracellular space, may act to increase weekly clearance of phosphate because serum phosphate levels before the next dialysis are higher.

Thus, with dialysis there must be a balance between adequate correction of acidosis (to reduce osteodystrophy) and avoidance of excessive alkalosis, which may cause postdialysis fatigue syndrome, impair phosphate removal, and favor metastatic calcification. It has been proposed that modeling the delivery of bicarbonate, with lower bicarbonate concentration during early dialysis to reduce intracellular shift of phosphate and higher bicarbonate during the last hour of dialysis to correct acidosis, may safely improve phosphate removal. To test this hypothesis under realistic operating conditions, the following study compared the metabolic consequences of standard, high, and modeled-bicarbonate conventional dialysis.

METHODS

The study was approved by the Western Sydney Area Health Service Research and Human Ethics Committees.
and conducted according to the principles set out by the National Health and Medical Research Council of Australia.

Patients

Twelve stable adult patients gave informed consent and were enrolled in the study. They were receiving standard bicarbonate hemodialysis at one satellite center, and had a predialysis serum bicarbonate (HCO₃⁻) level of < 20 mmol/L after a 2-day break. Three patients were subsequently dropped from the study because of failure to complete two of the treatment arms because of protocol violation (two patients) or diarrhea after ingesting oral bicarbonate.

All of the other nine patients remained stable throughout the study without any alteration of dialysis schedule or parameters (except bicarbonate), medications, or diet. Patients were dialyzed for 4 (seven patients) or 5 (two patients) h three times a week at blood flow rates of 225 to 250 mL/min (accurate to ± 5 mL/min), using cellulose acetate or hemophan dialyzers (sterilized with ethylene oxide and steam, respectively) of 1.1 to 1.3 m². Dialysis concentrations of calcium (1.3 or 1.5 mmol/L), magnesium, and potassium differed among patients, but for an individual patient were constant throughout the study. Dialysate acetate concentration was constant for each patient at 4 or 5 mmol/L.

Study Design

The study was a randomized double-crossover trial of three treatments. To avoid order effects, two patients each were to receive treatment by one of six possible sequences; the three dropouts were each from different sequences. The duration of each treatment arm was 4 wk, with the initial 2 wk a run-in or washout phase for titration of oral bicarbonate therapy. The treatments were: (1) standard-bicarbonate dialysis without oral bicarbonate, to maintain predialysis plasma HCO₃⁻ at 18 to 20 mmol/L. Dialysis bicarbonate concentration was determined before the study to achieve the target predialysis plasma bicarbonate without oral bicarbonate supplements. (Dialysate bicarbonate concentrations were 30, 32, and 34 mmol/L, respectively; in three, five, and one patients); (2) high-bicarbonate (40 mmol/L) dialysis, with oral bicarbonate supplements (840-mg capsules, 10 mmol Na⁺ per capsule) to maintain predialysis plasma HCO₃⁻ at 24 to 26 mmol/L; and (3) Modeled-bicarbonate (exponential increase from 28 mmol/L at 35 mmol/L at 3 h, and 40 mmol/L at 4 h) dialysis, with oral bicarbonate supplements to maintain predialysis plasma HCO₃⁻ at 24 to 26 mmol/L.

Measurements

Biochemical measurements were made during the second and third dialysis of the final week of each treatment. Samples were drawn hourly during dialysis and, where appropriate, before and after dialysis for analysis of: prefiltter plasma inorganic phosphate, urea, calcium, albumin, and bicarbonate levels by using a Hitachi 911 random access analyzer (Boehringer Mannheim, Castle Hill, NSW); prefiltter blood pH and bicarbonate levels by using a Nova stat 5 blood gas analyzer (Boehringer Mannheim, Castle Hill, NSW), and hematocrit; and postfilter phosphate, potassium, and hematocrit. Dialysate samples for phosphate and urea levels were taken hourly. Fasting plasma triglycerides, total cholesterol and HDL cholesterol were measured before the second dialysis of the final week, by using the Hitachi 911 random access analyzer.

Body weight was recorded before and after and ultrafiltration during each dialysis. Patients were specifically questioned about the following symptoms at each of the last two dialyses, and ranked symptoms on a Likert scale (0 = nil, 5 = maximum): tiredness, nausea, headache, and confusion.

Dialysate phosphate levels were measured with a Cobas Fara centrifugal analyzer (Roche Diagnostic Systems, Frenchs Forest, NSW) and by using the Roche Unimate 7 PHOS reagent with increased sample volume to measure the lower phosphate concentration in the dialysate fluid. Within-run assay imprecision was approximately 2%, expressed as percent coefficient of variation, at both low and high concentration; between-run imprecision was 4% at 92 μmol/L and 2% at 600 μmol/L. Each patient’s samples were analyzed on a single analytical run.

Biochemical data were analyzed for each of six dialyses in eight patients; data were lost on one of two high-bicarbonate dialyses in one patient.

Calculations

Dialysate clearance of phosphate was calculated by: (1) Direct Fick method (2), using the formula \( \frac{(C_{a}-C_{d})}{Q_{b}} \times (1-Hct)(1-R) \), where \( C_{a} \) and \( C_{d} \) are concentrations of phosphate in arterial and venous limbs of the dialyzer, respectively, \( Q_{b} \) is blood-flow rate, Hct is hematocrit, and R is recirculation. R was calculated by the low-flow method using the formula \( \frac{(C_{p}-C_{a})}{(C_{p}-C_{v})} \), where \( C_{a} \) and \( C_{v} \) are concentrations of urea in arterial and venous limbs and peripheral vein, respectively. The \( C_{p} \) sample was taken from the arterial line (after withdrawal of \( C_{a} \) and \( C_{v} \) samples) exactly 25 s after \( Q_{b} \) was reduced to 50 mL/min, after exactly 30 min of dialysis (9). The sampling time of 25 s was chosen to wash out recirculated blood (by first discarding 150% of the volume (12.5 mL) between the arterial needle and sampling point) and to avoid sampling after urea rebound had begun in arterial blood; and (2) Direct dialysate clearance, using the formula \( \frac{M}{C_{a}} = \frac{Q_{b} \times T \times C_{p}-C_{v}}{C_{a}} \), where M is the mass transfer of phosphate, \( Q_{b} \) is the dialysate flow, T is the time in min, and \( C_{a} \) and \( C_{v} \) are the concentrations of phosphate in the arterial limb of the dialyzer and dialysate, respectively. All dialysis effluent was collected each hour, and phosphate concentration measured in a thoroughly mixed sample. Phosphate rebound was defined as the difference between plasma phosphate at the end of and 2 h after dialysis. Efficiency of dialysis was also estimated by \( \frac{Kt}{V} \), by using the formula \( \frac{PRU.0.04}{(C_{p}-C_{a})/C_{a}} \times \frac{1}{1-Hct} \), where PRU = dialysate clearance, and \( C_{a} \) was concentration of the one

\[ \text{Body weight} = \text{total calcium} - (0.019 \times \text{albumin}) - (0.0091 \times \text{HCO}_3^-) - 0.10 \]  

based on factors known to influence calcium ionization. The formula was modified from that of Nordin et al. (13) to account for globulin and anion gap, which were not measured in this study. The concentration of tribasic inorganic phosphate (\( \text{PO}_4^{3-} \)) was estimated from the concentration of
inorganic phosphate and pH using published (14) equilibration constants for inorganic phosphate. As the concentration of \( \text{PO}_4^{3-} \) is extremely low at physiological pH, the risk factor (relative saturation ratio of hydroxyapatite) depends mainly on the concentrations of calcium and bicarbonate for its numerical value, but is limited mainly by the concentration of \( \text{PO}_4^{3-} \), which in turn depends primarily on pH.

Statistics

The primary variables were phosphate clearance and phosphate rebound, and secondary variables were urea clearance, other biochemical results, symptoms, and dialysis events. Data were stored and analysed using the Statistical Package for Interactive Data Analysis (SPIDA, Version 6.01, Macquarie University, Sydney). Differences among the three treatments were assessed by within-patient analyses using the paired t and Wilcoxon tests for parametric and nonparametric data, respectively, with a Bonferroni correction requiring \( P \leq 0.05 \div 3 \) to indicate significance. Values are expressed as mean ± standard error (mean ± SE).

RESULTS

There were no differences in clearance of phosphate, as calculated by the Direct Fick method among standard, high, and modeled bicarbonate conventional dialysis (Table 1), nor in clearance and mass transfer of phosphate as calculated by phosphate appearance in dialysate (Table 2). Plasma phosphate at all time points, the fall in plasma phosphate during the first hour of dialysis, and post-dialysis phosphate rebound were no different among the three treatments (Figure 1). The percentage reduction in serum phosphate levels during dialysis were similar (42 ± 3%, 40 ± 6%, and 39 ± 4% for standard, high, and modeled bicarbonate dialysis).

Plasma bicarbonate was significantly lower before, during, and 2 h after standard bicarbonate dialysis than with high or modeled bicarbonate dialysis, and during modeled versus high bicarbonate dialysis (Figure 2). Differences in plasma pH among the three treatment groups mirrored those of plasma bicarbonate (Table 3). More oral bicarbonate capsules were required during modeled versus high bicarbonate dialysis (2.8 ± 0.4 versus 1.4 ± 0.4/day, \( P = 0.04 \)).

Plasma total calcium was similar at each time point among the three treatments, and the apparent rise during dialysis was not statistically significant (Table 4). Thus plasma calcium-phosphate product fell similarly with each treatment (Table 4). Calculated plasma ionized calcium was similar at each time point, and appeared to rise from 1.30 ± 0.04 mmol/L before dialysis to 1.34 ± 0.03 at the end of dialysis, and to fall back to 1.30 ± 0.03 mmol/L 2 h after dialysis. Calculated plasma tribasic inorganic phosphate (\( \text{PO}_4^{3-} \), Table 4) and the estimated risk of metastatic calcification were no different among each of the three treatments (Figure 3).

Mass transfer of urea and \( \text{Kt/V} \) (Table 5), urea clearance, plasma urea, plasma potassium, and potassium rebound were no different among the three treatments. In each group, serum plasma albumin levels rose by approximately 3 g/L during dialysis from approximately 38 g/L before dialysis. Blood pressure fell similarly with each treatment during dialysis, and was only different between treatments before the last dialysis when systolic pressure was higher with standard than high bicarbonate (by 16 mm Hg) and diastolic higher with modelled than standard bicarbonate (by 10 mm Hg). Interdialytic weight gain (1.8 ± 0.2, 2.0 ± 0.2, and 2.0 ± 0.2 kg) and mean ultrafiltration (2.2 ± 0.2, 2.4 ± 0.2, and 2.4 ± 0.2 L/dialysis) were similar for standard, high, and modeled bicarbonate dialysis respectively. There were no differences in symptomatology and dialysis events with and patient preference for the three treatments. Four patients complained of mild (score 1/5) headaches (three with standard, one with modeled bicarbonate) and two of moderate (score 3 to 4/5) tiredness (one each with high and modeled bicarbonate).

DISCUSSION

Dialysis and acid-base balance have complex effects on phosphate metabolism. An important impediment to dialytic clearance of phosphate is its concentration in compartments other than extracellular fluid. Phosphate shifts from these deeper compartments during and after dialysis so that plasma phosphate reaches a steady state early in dialysis. The movement of phosphate into extracellular fluid may be impeded by alkalosis and dialysate buffer bases. Dialysis against a high dialysate bicarbonate concentration may be used to correct uremic acidosis, but carries the potential risk of reducing phosphate clearance and worsening metastatic calcification. Veech (8) and others (3) have proposed that modeling dialysate bicarbonate could be used to both increase phosphate clearance early in dialysis and correct acidosis late in dialysis. Dialysis machines with the capacity to model bicarbonate have been available commercially for several years, but the clinical utility of this technology, which increases the cost above that of standard dialysis machines by approximately 15%, has not been appraised critically.

In the present study, phosphate clearance, calculated by its disappearance from the blood compart-
TABLE 2. Hourly and total mass transfer of phosphate (mmol) during standard, high, and modeled bicarbonate dialysis, as assessed by direct measurement of dialysate phosphate.\(^a\)

<table>
<thead>
<tr>
<th>Dialysate Bicarbonate</th>
<th>Mass Transfer of Phosphate</th>
<th>TOTAL(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Standard</td>
<td>4.37 ± 0.68</td>
<td>3.53 ± 0.48</td>
</tr>
<tr>
<td>High</td>
<td>4.21 ± 0.78</td>
<td>3.31 ± 0.54</td>
</tr>
<tr>
<td>Modeled</td>
<td>3.98 ± 0.76</td>
<td>3.09 ± 0.50</td>
</tr>
</tbody>
</table>

\(^a\) The values are means of those obtained during the second last and last dialysis of each treatment. There were no differences between respective mass transfer during the second last and last dialyses.

\(^b\) Excludes last hour of two patients who were dialysed for 5 h. There were no differences among the three treatments. Mean ± SE.

Figure 1. Mean plasma phosphate (P\(_i\)) during and phosphate rebound after the last treatment with standard (S, solid line), high (H, interrupted line), and modeled (M, dotted line) dialysis.

Figure 2. Mean plasma bicarbonate (HCO\(_3^-\)) during and after the last treatment with standard (solid line), high (interrupted line), and modeled (dotted line) dialysis. Significantly different from other two values (*).
TABLE 3. Prefilter blood pH before and during the last treatment with standard, high, and modeled bicarbonate dialysis

<table>
<thead>
<tr>
<th>Dialysate Bicarbonate</th>
<th>0 h</th>
<th>1 h</th>
<th>2 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>7.38</td>
<td>7.40</td>
<td>7.41</td>
<td>7.45</td>
</tr>
<tr>
<td>High</td>
<td>7.41</td>
<td>7.44</td>
<td>7.46</td>
<td>7.51</td>
</tr>
<tr>
<td>Modeled</td>
<td>7.40</td>
<td>7.42</td>
<td>7.42</td>
<td>7.48</td>
</tr>
</tbody>
</table>

*Significantly different from high. SE for each value was 0.01.

toxicity of overcorrecting acidosis. Alkalosis may contribute to the so-called postdialysis fatigue syndrome, and favor metastatic calcification (11). In this study there was no evidence of the former. High and modeled bicarbonate dialysis were tolerated as well as standard bicarbonate dialysis. Moreover, blood pressure and fluid control were not worsened by the sodium load of oral bicarbonate supplementation.

There was nothing to suggest that the risk of metastatic calcification was increased by raising dialysate bicarbonate within the range described in this study. By all of the criteria by which the risk of metastatic calcification could be judged, there was no difference between standard and high or modeled bicarbonate dialysis. Plasma inorganic phosphate and estimated plasma tribasic inorganic phosphate (the phosphate component of hydroxyapatite) were no different at any time point among the three treatments. Phosphate rebound, a result of continued shift of phosphate into extracellular fluid after dialysis and perhaps a measure of the intracellular shift of phosphate during dialysis, was also no different. Plasma total calcium levels tended to rise equally with each treatment, as did estimated plasma ionized calcium levels.

Calcification risk is frequently estimated by the calcium-phosphate product, which was less than 3.5 mmol²/L² at all time points in this group of compliant patients. This is a crude measure at best, as it ignores

![Figure 3. The estimated risk factor for metastatic calcification with standard (clear bar), high (gray) and modeled (black) bicarbonate dialysis. The risk factor, which was the mean relative saturation ratio for hydroxyapatite before and after dialysis, was no different between treatments.](image)

the factors that influence calcium ionization, and the influence of pH on the equilibrium of different species of inorganic phosphate (14), and of bicarbonate on the formation of hydroxyapatite, the main component of vascular metastatic calcification (13). A risk factor for metastatic calcification was estimated by taking these influences into account, and was no different among the three treatments. Several points must be appreciated in interpreting these results. The risk factor is an

TABLE 4. Total plasma calcium, calcium-phosphate product, and estimated tribasic inorganic phosphate (PO₄³⁻) concentration before, during, and 2 h after the last treatment with standard, high, and modeled bicarbonate dialysis

<table>
<thead>
<tr>
<th>Dialysate Bicarbonate</th>
<th>Plasma Total Calcium (mmol/L)</th>
<th>Plasma Calcium-Phosphate Product (mmol²/L²)</th>
<th>Estimated Plasma PO₄³⁻ (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-post</td>
<td>0-post</td>
<td>0-post</td>
</tr>
<tr>
<td>Standard</td>
<td>2.37 ± 0.07</td>
<td>3.32 ± 0.31</td>
<td>4.26 ± 0.26</td>
</tr>
<tr>
<td>High</td>
<td>2.42 ± 0.05</td>
<td>2.46 ± 0.07</td>
<td>4.33 ± 0.35</td>
</tr>
<tr>
<td>Modeled</td>
<td>2.43 ± 0.05</td>
<td>2.48 ± 0.06</td>
<td>4.92 ± 0.33</td>
</tr>
</tbody>
</table>

*There were no differences between treatments. Mean ± SE.
TABLE 5. Hourly and total mass transfer of urea (mmol) and Kt/V during standard, high, and modeled bicarbonate dialysis, as assessed by direct measurement of dialysate urea and from percentage urea reduction respectively.a

<table>
<thead>
<tr>
<th>Hours</th>
<th>Dialysate Bicarbonate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mass Transfer of Urea</td>
<td>Kt/V</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>144.0 ± 13.3</td>
<td>143.7 ± 14.8</td>
</tr>
<tr>
<td></td>
<td>114.4 ± 9.6</td>
<td>113.1 ± 9.6</td>
</tr>
<tr>
<td></td>
<td>80.4 ± 6.6</td>
<td>85.3 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>61.3 ± 6.1</td>
<td>67.2 ± 7.7</td>
</tr>
<tr>
<td>TOTALb</td>
<td>409.0 ± 34.0</td>
<td>409.2 ± 40.5</td>
</tr>
</tbody>
</table>

a The values are means of those obtained during the second last and last dialysis of each treatment. There were no differences between respective values from the second last and last dialyses.

b Excludes last hour of two patients who were dialysed for 5 h. There were no differences among the three treatments. Mean ± SE.

estimate made on the basis of static plasma concentrations (and estimated rather than measured ionized calcium), does not disprove a dynamic difference at the tissue level, and has not been validated against tissue hydroxyapatite concentrations. Although it ignores other factors that influence metastatic calcification and were not measured in the present study, there is no logical reason to suspect any additional perturbation which would influence calcification more with one treatment than the other. Moreover, the main limiting species for hydroxyapatite formation, tribasic phosphate, was estimated to be almost identical before and after each of the treatments. Thus, as long as serum calcium and phosphate levels are controlled, standard, high, and modeled bicarbonate dialysis, as described, are equal in their effect on fluid and blood pressure control, and in their potential for causing metastatic calcification. High and modeled bicarbonate dialysis are equally potent and safe in their ability to correct uremic acidosis, and the additional expense of modeling technology must be questioned if utilized only for its effect on phosphate and acid-base balance.

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REFERENCES