Phosphate Kinetics During High-Flux Hemodialysis

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(J. Am. Soc. Nephrol. 1993; 4:1214-1218)

ABSTRACT
Phosphate clearance by polysulfone (PS) and cuprophane (CU) membranes and the relationship of peridialytic changes in serum phosphate with those of serum-ionized calcium, parathyroid hormone (PTH), and insulin were studied in six stable patients undergoing chronic hemodialysis (HD). Dietary phosphate intake was 25.7 mmol/day, and total dose of elemental calcium was 3.2 g/day. Patients were dialyzed for 2 to 4 h, once with each membrane. Serum phosphate levels fell precipitously during the first hour of HD with both dialyzers, from 1.42 and 1.49 mM to nadirs of 0.53 and 0.69 mM for PS and CU, respectively. Phosphate levels began to increase either late in HD or at the end of HD and, by 4 h post-HD, did not differ from predialysis values. Total mass transfer of phosphate was greater during the first hour (3.4 and 3.2 mmol for PS and CU, respectively) than during the remainder of HD (2.4 and 2.6 mmol/h). There were no significant differences in intradialytic serum phosphate changes, postdialytic phosphate rebound, or total phosphate removal between the two dialyzers. Ionized calcium increased by 0.11 mM, and PTH was suppressed to 40 to 50% of baseline values during dialysis with either membrane. Although phosphate removal continued for the duration of dialysis, serum phosphate did not continue to decrease, either reaching an apparent steady state or beginning to rebound, even during dialysis. This suggests active phosphate mobilization from a pool other than the extracellular fluid and demonstrates the inadequacy of a one-compartment model to explain these data. Further, these data do not support the regulation of intradialytic phosphate mobilization by serum PTH or insulin. The transient, but profound, intradialytic hypophosphatemia may serve as a stimulus for as-yet-uncharacterized homeostatic mechanisms.

Key Words: Phosphorus, clearance, hemodialysis

Sustained hyperphosphatemia, common in patients with ESRD, leads to secondary hyperparathyroidism and, ultimately, to renal osteodystrophy. Control of serum phosphate depends on dietary phosphate restriction and the use of phosphate-binding agents. These approaches are inadequate in many patients. Phosphate-restricted diets may lead to protein-calorie malnutrition. Aluminum-based phosphate binders often result in bone, central nervous system, and hematologic toxicity; calcium-containing binders may lead to hypercalcemia. Interest in phosphate removal by hemodialysis (HD) has increased with the advent of more efficient dialysis techniques (1).

Serum phosphate indeed declines significantly during HD (2-11). There is, in addition, a marked postdialytic rebound of serum phosphate levels (2-5,7-9,12). The clinical significance of dialytic phosphate removal is unclear, because it does not appear to influence predialysis levels (11,12), although it may affect calcium homeostasis (5). Bicarbonate-containing dialysate may facilitate phosphate removal, though conflicting results have been reported (6,7,12,13).

Because newer synthetic dialysis membranes exhibit high phosphate clearances in vitro, we sought to compare phosphate clearance by polysulfone (PS) and cuprophane (CU) membranes, in vivo. In these studies, conducted in patients with comparable diets and dialysis prescriptions, we also attempted to assess the relationship of peridialytic changes in serum phosphate with those of serum-ionized calcium, parathyroid hormone (PTH), and insulin.

METHODS

Clinical Methods

Six stable nondiabetic patients, five women, ages 36 to 52 (mean, 43 yr), 50 to 71 kg (mean, 64 kg), undergoing chronic high-flux HD participated in this study after granting written, informed consent. Dietary phosphate intake was 795 ± 102 mg/day (25.7 ± 2.9 mmol/day), as assessed by patient-recorded
food diaries kept for 2 wk before the study. Only calcium-containing phosphate binders (3.2 ± 2.8 g of elemental calcium) were used. Patients were excluded if serum phosphate was more than 2.0 mM or calcium was less than 1.9 mM during the 2 wk before the study or if either aluminum-related bone disease or severe secondary hyperparathyroidism was known or clinically suspected. All dialysis treatments were delivered with Cobe Centry System 3 HD machines (Cobe Laboratories, Denver, CO) with 35 mM bicarbonate–3.0 mEq/L calcium dialysate. After an overnight fast, patients ate a 225-mg phosphate meal just before dialysis, then remained fasting during dialysis and for 4 h afterwards. Patients were dialyzed for 2.5 to 4 h at a blood flow (Qb) of 400 to 450 mL/min; dialysis prescription was based on single-pool urea kinetic modeling (14,15). Dialysate flow rate ranged from 550 to 640 mL/min (coefficient of variance [CV] ± 5%). Each patient was studied with both PS (F-80; 1.9 m²; Fresenius AG, Bad Homburg, Germany) and CU (CF-2308; 1.3 m²; Baxter, Deerfield, IL) dialyzers. Patients thus served as their own controls and were studied on two occasions during the same week. Arterial samples for the determination of serum phosphate and blood-ionized calcium were drawn at the beginning of HD, every 15 min for 1 h, then every 30 min until the end of HD. Dialysate was sampled at the same times as blood. After dialysis, samples were drawn every 15 min for the first hour, then every 30 min until 4 h post-HD. PTH and insulin levels were assessed at the beginning of HD, mid-HD, end-HD, and 4 h post-HD. Serum urea was determined pre-HD and post-HD.

Analytical Methods

Ionized calcium and pH were measured immediately in heparinized whole blood. Blood was centrifuged, and serum was separated and frozen for later determination of phosphate, PTH, and insulin. Blood-ionized calcium was measured with an ion-specific electrode (NOVA II; Nova Biomedical, Newton, MA), and pH measurements were made with a Beckman Phi 71 pH meter (Beckman Instruments, Fullerton, CA). Inorganic phosphate was determined by the microassay method of Lindberg and Ernster (16). PTH was measured by a whole-molecule immunoradiometric assay (N-tact® PTH IRMA; Incstar, Stillwater, MN), and insulin was measured by double antibody immunorosay (17). Serum urea was determined by a urease method (Ektachem; Eastman Kodak, Rochester, NY).

Access recirculation was calculated as R = (Cp – Ca)/(Cp – Cw), where R is percent recirculation, Cw is urea concentration of peripheral venous blood, and Ca and Cp are urea concentration of blood drawn from the arterial and venous limbs of the dialyzer circuit, respectively. Dialyzer (blood-side) clearance (CL) of phosphate was calculated by the direct Fick principle according to the following equation:

\[
CL = \frac{[(C_A - C_v)/C_A] \cdot Q_d (1 - Hct)(1 - R)}{(Q_d T)}
\]

where C_A and C_v are phosphate concentration measured in samples drawn from the arterial and venous limbs of the dialyzer, respectively, and Hct is hematocrit. The mass transfer (MT) of phosphate into dialysate during dialysis was calculated as MT = (Q_d T) (C_A), where T is time (in minutes) and C_A is phosphate concentration in dialysate. Dialysate clearance was then calculated as CL_d = (MT)/C_A. The fractional urea clearance, Kt/V urea was calculated for each dialysis by the method of Daugirdas (15). Data are reported as mean ± SE. Pairwise comparisons used t tests, whereas other comparisons used randomized one-way analysis of variance with Neuman-Keul’s multiple-range test (STATPAK; Northwest Analytical, Portland, OR). P < 0.05 was considered significant.

RESULTS

Serum phosphate declined precipitously early in dialysis (Figure 1; Table 1), reaching a nadir in 30 to 150 min. Phosphate levels began to increase either late in HD or at the end of HD. By 4 h post-HD, serum phosphate did not differ from predialysis values. There were no significant differences in either intradialytic serum phosphate changes or phosphate rebound, comparing PS and CU dialyses.

Phosphate was cleared more efficiently by PS than by CU dialyzers, when assessed by the direct Fick principle (Table 2). However, dialyzer phosphate clearance did not differ when corrected for differences in membrane surface area. Total phosphate removal (MT) was greater during the first hour than during the remainder of HD but did not differ significantly between PS and CU dialyzers. Phosphate clearances calculated by the Fick principle significantly exceeded peak values calculated with first-hour MT data, which averaged 82 ± 8 and 78 ± 5 mL/min for PS and CU, respectively.

As expected, ionized calcium increased and PTH was suppressed during HD, returning toward predialysis values by 4 h post-HD (Table 3). Insulin, which may contribute to the regulation of cellular phosphate uptake, did not change significantly during dialysis. Predialysis insulin levels were 92 ± 54 and 66 ± 14 μU/mL (PS and CU, respectively; N = 3). These levels fell to 50 ± 35 and 40 ± 8 μU/mL by the end of dialysis and were suppressed further to 21 ± 12 and 19 ± 2 μU/mL at 4 h post-HD, after prolonged fasting.

DISCUSSION

During dialysis with either PS or CU, phosphate removal resulted in an early and profound fall in
serum phosphate. Although phosphate removal continued at a lower rate for the duration of dialysis, serum phosphate did not continue to decrease, either reaching a plateau or beginning to rebound even during dialysis. Other workers have noted similar intradialytic decreases of serum phosphate as well as postdialytic rebound (2-4, 7-9, 12). Although Pog-glitsch and coworkers (8) reported that serum phosphorous did not fall below a normal range of 0.8 to 1.4 mM, even with prolonged HD or hemofiltration, our results suggested no clear lower limit to intradialytic serum phosphorous. All patients exhibited

**TABLE 1. Serum phosphate levels**

<table>
<thead>
<tr>
<th>Serum Phosphate (mM)</th>
<th>Pre-HD</th>
<th>Nadir</th>
<th>End-HD</th>
<th>4 h Post-HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>1.42 ± 0.30</td>
<td>0.53 ± 0.14*</td>
<td>0.53 ± 0.07*</td>
<td>1.25 ± 0.09*</td>
</tr>
<tr>
<td>CU</td>
<td>1.49 ± 0.20</td>
<td>0.69 ± 0.19*</td>
<td>0.72 ± 0.07*</td>
<td>1.49 ± 0.11*</td>
</tr>
</tbody>
</table>

* P < 0.01 when compared with predialysis value.
* Not significant when compared with predialysis value.

**TABLE 2. Phosphate and urea kinetics**

<table>
<thead>
<tr>
<th></th>
<th>PS</th>
<th>CU</th>
</tr>
</thead>
<tbody>
<tr>
<td>P clearance (mL/min)</td>
<td>167 ± 12</td>
<td>106 ± 6*</td>
</tr>
<tr>
<td>P clearance mL/min·m²</td>
<td>89 ± 12</td>
<td>81 ± 10</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.40 ± 0.08</td>
<td>1.27 ± 0.12</td>
</tr>
<tr>
<td>Total P MT (mmol)</td>
<td>7.5 ± 2.2</td>
<td>8.2 ± 3.2</td>
</tr>
<tr>
<td>P MT (first hour) (mmol)</td>
<td>3.4 ± 1.0</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>P MT (subsequent hours) (mmol)</td>
<td>2.4 ± 0.6</td>
<td>2.6 ± 1.3</td>
</tr>
</tbody>
</table>

* Kt/V: fractional urea clearance.
* P < 0.05 compared with PS.
early intradialytic decrements in serum phosphate, to values as low as 0.27 mM.

Phosphate MT continued during late dialysis, even though serum phosphate was no longer decreasing. This is consistent with phosphate mobilization from a pool other than the extracellular fluid (12). The fact that rebound sometimes occurred during dialysis, as previously reported by other workers (3,8), suggests active, rather than merely passive, phosphate mobilization. Sugisaki et al. attempted to describe such kinetics using a one-compartment open model but had to invoke an increasing "phosphate generation rate" to model the plateau and rebound data (2,3). On the basis of the ability of intradialytic phosphate infusion to inhibit the usual increase of plasma (total) calcium, Carney and Gillees speculated that phosphate loss during dialysis leads to the transfer of both phosphate and calcium from an exchangeable bone pool (5). Haas et al., studying hemofiltration, argued against bone as a phosphate source and suggested that active phosphate mobilization was related to transcellular potassium fluxes (12). Hou and co-workers found that variations in dialysate calcium concentrations had no effect on intradialytic phosphate removal but obtained little postdialytic data, precluding a more complete analysis of phosphate rebound kinetics (4). A single-pool model was inadequate to describe our data; we speculate that falling serum phosphate levels during dialysis may lead to the loss of supersaturation with respect to a phosphate salt, providing the driving force for its mobilization from tissue, bone, or extraskeletal deposits.

Phosphate clearance was greater when assessed by the direct Fick principle than when calculated from dialysate MT data, i.e., blood-side clearance exceeded dialysate clearance. This suggests that, even during the first hour of dialysis, phosphate removal was limited more by its mobilization or intercompartmental transfer than by dialyzer efficiency. Thus, clearance did not differ between CU and PS dialyzers, either when corrected for membrane surface area or when calculated by the use of MT data.

Phosphate was cleared more efficiently early in dialysis, when serum phosphate was highest. Indeed, others have reported that the dialytic removal of phosphate varies directly with its predialysis serum levels (2,9). By study design, predialysis serum phosphate did not exceed 2 mM in our patients, potentially limiting the contribution of dialytic phosphate removal. Other workers (4,5,11,13), all studying patients with higher predialysis phosphate than those in this study, reported significantly higher values of phosphate MT.

As expected, blood-ionized calcium remained elevated throughout dialysis. Failure to suppress PTH during dialysis might have resulted in the mobilization of both calcium and phosphorus from bone. However, PTH was significantly suppressed during dialysis, returning to values not significantly different from baseline by 4 h postdialysis. Likewise, because insulin mediates intracellular phosphate movement, elevated insulin levels during dialysis might have resulted in lower intradialytic serum phosphate. However, insulin decreased during and after dialysis in these fasting patients. Thus, our data do not support the regulation of phosphate mobilization by intradialytic changes in PTH or insulin.

We were surprised by the degree of intradialytic hypophosphatemia, which exceeded that reported previously (2,4,7,11,12). Although the apparent absence of adverse sequelae due to hypophosphatemia presumably relates to its transient nature, it is likely that this profound abnormality serves as a stimulus for as-yet-uncharacterized homeostatic mechanisms.

ACKNOWLEDGMENTS

We thank T. Gember, M. Carey, C. Wolgemuth, L. Huang, and the University of Chicago Chronic Dialysis Unit Staff for excellent clinical support. Our thanks also go to E. Kaplan and K. Polonsky for generously providing PTH and insulin assays and to S. Sprague and J. Aspin for their helpful comments. Supported in part by the Children’s Research Foundation, Wyler Children’s Hospital, Chicago.

TABLE 3. Calcium, pH, and PTH changes during and after dialysis

<table>
<thead>
<tr>
<th></th>
<th>Pre-HD</th>
<th>Mid-HD</th>
<th>End-HD</th>
<th>4 h Post-HD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ca^2+ (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>1.13 ± 0.04</td>
<td>1.23 ± 0.03^a</td>
<td>1.21 ± 0.04^a</td>
<td>1.09 ± 0.03</td>
</tr>
<tr>
<td>Cu</td>
<td>1.00 ± 0.03</td>
<td>1.09 ± 0.03^a</td>
<td>1.12 ± 0.04^a</td>
<td>1.04 ± 0.03</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>7.28 ± 0.03</td>
<td>7.40 ± 0.03^a</td>
<td>7.44 ± 0.04^a</td>
<td>7.36 ± 0.03^b</td>
</tr>
<tr>
<td>CU</td>
<td>7.35 ± 0.04</td>
<td>7.41 ± 0.03</td>
<td>7.46 ± 0.02^a</td>
<td>7.40 ± 0.02^b</td>
</tr>
<tr>
<td><strong>PTH (pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>161.7 ± 43.9</td>
<td>50.7 ± 17.9^bc</td>
<td>51.7 ± 16.6^ac</td>
<td>145 ± 27.7^c</td>
</tr>
<tr>
<td>Cu</td>
<td>223.7 ± 70.4</td>
<td>39.1 ± 14.3^ac</td>
<td>41.5 ± 13.6^ac</td>
<td>102.8 ± 8.4^c</td>
</tr>
</tbody>
</table>

^a P < 0.01 when compared with predialysis.
^b P < 0.05 when compared with predialysis.
^c Percentage of baseline.
REFERENCES