Kinetic Model of Phosphorus Mobilization during and after Short and Conventional Hemodialysis

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Summary

Background and objectives The kinetics of plasma phosphorus (inorganic phosphorus or phosphate) during hemodialysis treatments cannot be explained by conventional one- or two-compartment models; previous approaches have been limited by assuming that the distribution of phosphorus is confined to classical intracellular and extracellular fluid compartments. In this study a novel pseudo one-compartment model, including phosphorus mobilization from a large second compartment, was proposed and evaluated.

Design, setting, participants, & measurements Clinical data were obtained during a crossover study where 22 chronic hemodialysis patients underwent both short (2-hour) and conventional (4-hour) hemodialysis sessions. The model estimated two patient-specific parameters, phosphorus mobilization clearance and phosphorus central distribution volume, by fitting frequent intradialytic and postdialytic plasma phosphorus concentrations using nonlinear regression.

Results Phosphorus mobilization clearances varied among patients (45 to 208 ml/min), but estimates during short (98 ± 44 ml/min, mean ± SD) and conventional (99 ± 47 ml/min) sessions were not different (P = 0.74) and correlated with each other (concordance correlation coefficient ρc of 0.85). Phosphorus central distribution volumes for each patient (short: 11.0 ± 4.2 L and conventional: 11.9 ± 3.8 L) were also correlated (ρc of 0.45).

Conclusions The reproducibility of patient-specific parameters during short and conventional hemodialysis treatments suggests that a pseudo one-compartment model is robust and can describe plasma phosphorus kinetics under conditions of clinical interest.

Introduction

Hyperphosphatemia in end-stage renal disease patients has been associated with greater risk of mortality (1,2), primarily because of cardiac-related causes (3). Such associations have been demonstrated among various countries and over time (4,5). Although the physiologic mechanisms involved remain incompletely understood, hyperphosphatemia and the use of calcium-based oral phosphate binders have been linked to rapid progression of coronary calcification (2,6,7), increased stiffness of the arterial wall, and high blood pressure (8).

Control of serum phosphorus concentrations in hemodialysis (HD) patients usually requires both the daily use of oral binders to inhibit intestinal absorption of dietary phosphate (9) and the removal of phosphate by HD treatments. Despite this dual approach, hyperphosphatemia is prevalent because typical Western diets contain high phosphate content (10). Efforts have attempted to increase dialytic removal of phosphate during thrice-weekly therapy by various methods, often without substantial improvements (11–15). The only HD prescription parameter shown to consistently reduce serum phosphorus concentrations is the use of long treatment durations, both during thrice-weekly HD (16,17) and during HD treatments applied more frequently (18–20).

A robust and practical phosphorus kinetic model is necessary to better understand the physiologic limitations to dialytic removal of phosphorus and to effectively modify new HD treatment modalities on an individual patient basis. It has long been known that the kinetics of phosphorus are more complex than those for urea (21,22). More complicated, multi-compartment models have also been applied; however, these have been either inadequate (23) or very complex (24). In this study, we propose and evaluate a novel pseudo one-compartment kinetic model consisting of an accessible compartment and a second large compartment that is inaccessible directly by the dialyzer but from which phosphorus is continuously mobilized as a function of predialytic and instantaneous plasma phosphorus levels.

Materials and Methods

Patients The study subjects were 22 chronic hemodialysis patients undergoing thrice-weekly maintenance HD
at two separate dialysis units within the University of Utah Dialysis Program. Patients who were medically unstable, hepatitis B-positive, hepatitis C-positive, HIV-positive, prisoners, pregnant, mentally disabled, or with hematocrit less than 28% were excluded. Patient age was 61 ± 18 (mean ± SD) years. Sixteen patients were male. Fourteen patients used native arteriovenous fistulas, six used synthetic arteriovenous grafts, and two used catheters for vascular access. Twenty-one patients were Caucasian, and one was Asian. Patients had been previously treated by maintenance hemodialysis for an average of 43 months before the study began (range 8 to 115 months). The protocol of this study was approved by the Institutional Review Board at the University of Utah, and all patients gave written, informed consent. Of the 22 patients that participated in this study, one was excluded from analysis because of a missing plasma sample at the end of the treatment.

**Clinical Study Procedures**

Before both study treatment sessions, a predialytic blood sample was collected from the vascular access. Additional samples were collected from the arterial blood tubing of the extracorporeal circuit at 30, 60, 120, and 180 minutes during CHD sessions and at 30, 60, and 90 minutes during the SHD sessions. For direct determination of dialyzer phosphate clearance, samples were taken from the dialysate outflow at 60 minutes from the start of treatment. Blood and dialysate samples were assayed for phosphorus concentration. At the end of each treatment, the blood flow rate was reduced to 120 ml/min, the dialysate flow was stopped, the ultrafiltration rate was set to the minimum setting, and postdialytic blood samples were collected after 10 seconds and 2, 10, 30, and 60 minutes from the arterial blood tubing.

New high-flux dialyzers (Optiflux F160NR or F200NR; Fresenius North America, Ogden, UT) were used with blood, dialysate, and ultrafiltration flow rates routinely prescribed for the respective patients. Nominal blood and dialysate flow rates were identical during SHD and CHD treatment sessions for each patient. During all treatment sessions, the actual blood flow rate was measured using the HD01 monitor (Transonic Systems, Ithaca, NY).

**Analytical Assays**

All of the samples were allowed to stand at room temperature for 30 to 60 minutes without any additional anticoagulant or preservatives. The samples were then centrifuged, and the plasma (or serum) was stored at −70°C until assayed. Plasma phosphorus was measured using an automated analyzer (Beckman CX7; Beckman Coulter, CA). Phosphorus concentrations in dialysate were often too low to be analyzed using routine methods and therefore were determined using the method described by Chen et al. (25) after calibration to the automated analyzer.

**Kinetic Model**

Two mathematically equivalent schematic representations of the proposed phosphorus kinetic model are shown in Figure 1. In this model, phosphorus is uniformly distributed within an accessible compartment of volume $V$, also called the central distribution volume, with a phosphorus concentration $C$. The entire central distribution volume is assumed to be in equilibrium with plasma during the intradialytic and postdialytic periods. Phosphorus mobilization into this compartment occurs from a second large compartment inaccessible to the dialyzer (Figure 1A). The inaccessible compartment represents all of the internal phosphorus pools combined; its physiologic identity is poorly defined but not relevant in this analysis. Because of its relatively large size, phosphorus concentration in this compartment was assumed to be constant and equal to the predialytic plasma phosphorus concentration ($C_{\text{PRE}}$). Because there are no time-dependent changes to the phosphorus concentration or the volume of the inaccessible compartment, the two-compartment representation is mathematically identical to the pseudo one-compartment model (Figure 1B). In either case, phosphorus is assumed to be removed during HD treatments from the accessible compartment at a rate proportional to the dialyzer phosphate clearance ($K_{\text{DP}}$). The rate of phosphorus mobilization
into the accessible compartment is described as the difference between predialytic and instantaneous plasma phosphorus levels multiplied by the phosphorus mobilization clearance (KM). Analogous to an intercompartmental mass transfer coefficient, KM is assumed to be constant and identical during the treatment and the postdialytic rebound periods.

Changes in phosphorus concentration (C) and central distribution volume (V) during and shortly after an HD session are represented by Equations 1 and 2,

$$\frac{d(VC)}{dt} = KM(C_{PRE} - C) - ΘK_D C$$ (Eq. 1)

$$\frac{dV}{dt} = -ΘQ_{UF}$$ (Eq. 2)

where t is treatment time, Θ is a variable that indicates whether the dialysis treatment is taking place (Θ = 1) or not (Θ = 0), KD is the dialyzer phosphate clearance, and QUF is the ultrafiltration rate calculated by the difference between predialytic and postdialytic body weight divided by treatment time and is assumed to be constant during the treatment. The ultrafiltration rate during the postdialytic period was assumed to be zero; thus, the central distribution volume was modeled as constant during this period. The kinetic model described above also assumes that all fluid removed during the treatment is derived from the accessible compartment. Generation of phosphorus caused by dietary intake and residual renal clearance of phosphorus were neglected.

Dialyzer clearance of phosphate was assumed to be constant during the treatment and was calculated as shown in Equation 3, where CpD is the concentration of phosphorus in the dialysate outflow and Qd is the dialysate flow rate.

$$KM = \frac{C_{D}Q_{D}}{C(t = 60)}$$ (Eq. 3)

Postdialytic rebound was expressed as a percentage and calculated using Equation 4, where T is the treatment duration.

$$\% \text{ rebound} (t) = \frac{C(t + T) - C(T)}{C(T)} \times 100$$ (Eq. 4)

Parameter Estimation

Model equations (Equations 1 and 2) were integrated numerically using the fourth-order Runge-Kutta method, and the values of phosphorus mobilization clearance (KM) and predialytic central distribution volume (VPRE) for each patient were determined via nonlinear regression or least-squares fitting to measured plasma phosphorus concentrations. Because postdialytic body weights during SHD and CHD were not expected to be identical because of the study design (patients were not dialyzed to the dry weight at the end of the SHD treatment), V values were reported as predialytic values. Assuming comparable errors in each concentration measurement, the predialytic plasma phosphorus concentration was also estimated simultaneously. SHD and CHD data were fit separately resulting in two sets of KM and VPRE values for each patient.

A scientific computational software package (lsqnonlin routine in MATLAB v2008a, Mathworks, Natick, MA) was used to perform nonlinear least-squares fitting. Nonlinear least-squares minimizes the sum of square errors of differences between the measured and modeled plasma phosphorus concentrations. The standard error (SE) for each estimated parameter was calculated using standard methods.

Statistical Analyses

Comparisons among measured values and parameter estimates during SHD and CHD were computed using paired t tests. A P value of less than 0.05 was considered statistically significant. Comparisons of estimated parameters for SHD and CHD were also performed by calculating the respective concordance correlation coefficient (ρc) (26,27). The coefficient of determination (R²) was calculated according to Equation 5 to assess the goodness of fit to clinical data, where n is the total number of blood samples collected from a patient, Cmean and Cmod are the measured and modeled plasma phosphorus concentrations of the ith sample, and Cmean is mean value of measured plasma phosphorus concentration.

$$R² = 1 - \frac{\sum_{i=1}^{n}(C_{i}^{mod} - \bar{C}_{mean})^2}{\sum_{i=1}^{n}(C_{i}^{mean} - \bar{C}_{mean})^2}$$ (Eq. 5)

Results

Treatment and patient parameters for SHD and CHD sessions are presented in Table 1. These measured parameter values were expected on the basis of the study design. Total fluid removed per session was less for SHD because of its shorter duration compared with CHD.

Figure 2 shows the average plasma phosphorus concentrations during SHD and CHD. In both cases, a rapid decrease was observed within the first 2 hours of treatment. Further dialysis during CHD resulted in plasma phosphorus levels reaching an approximate steady state that persisted until the treatment was terminated. Intradialytic plasma phosphorus concentrations during SHD and CHD were not different at coinciding time points. As shown in Figure 3, the percent rebound during postdialytic period did not differ between CHD and SHD. This contrasts with postdialytic rebound kinetics of urea where percentage of rebound after the SHD session was 27% greater compared with the CHD session as reported elsewhere (28).

An example least-squares fit to the measured plasma phosphorus concentrations is shown in Figure 4. Modeled and measured values were in good agreement during both the intradialytic and postdialytic periods (R² = 0.95 for SHD and R² = 0.93 for CHD). Estimated parameters for this patient were similar for SHD and CHD (SHD: KM = 10.9 L, VPRE = 76 ml/min versus CHD: VPRE = 10.8 L, KM = 93 ml/min) and estimates had good precision (SE for KM: 11 and 14 ml/min versus SE for VPRE: 1.4 and 1.4 L for SHD and CHD, respectively).
Table 2 shows a detailed summary of the estimated parameter values for all patients. Mean values for $K_M$ were 98/44 ml/min (mean SD) for SHD and 99/47 ml/min for CHD. Mean values for $V_{PRE}$ were 11.0/4.2 L for SHD and 11.9/3.8 L for CHD, or in terms of percent of postdialytic body weight, they were 13.6/4.0% for SHD and 15.3/5.5% for CHD.

An additional comparison of estimated parameters between SHD and CHD is shown in Figure 5. Parameter values determined from SHD and CHD sessions were correlated with each other (concordance correlation coefficient: 0.85 for $K_M$ and 0.45 for $V_{PRE}$). When compared statistically, the values determined during SHD and CHD were not different from each other ($P = 0.74$ for $K_M$ and $P = 0.34$ for $V_{PRE}$).

Discussion
The time dependence of plasma phosphorus concentration during HD treatments and the postdialytic rebound period reported in this study are consistent with many of those previously published. Intradialytic kinetics of plasma phosphorus have been previously characterized by an early, rapid decrease followed by a period of relatively constant concentration (21,29), in some cases leading to a rebound even before dialysis is terminated (21,29,30). During the postdialytic period, plasma phosphorus concentration increases rapidly, achieving predialytic levels within 4 to 8 hours (30–32). Although some patients in our study had an increase in plasma phosphorus concentration before the end of the CHD treatment, these increases were very modest, such that there was no definitive evidence of rebound before the end of the CHD treatment in the com-
The parameter estimates are expressed as estimated values ± standard error. $K_M$, phosphorus mobilization clearance; $V_{PRE}$, predialytic central distribution volume for phosphorus.

Table 2. Estimated values of patient parameters from short hemodialysis (SHD) and conventional hemodialysis (CHD) sessions

<table>
<thead>
<tr>
<th>Patient No</th>
<th>$K_M$ (SHD (ml/min))</th>
<th>$V_{PRE}$ (SHD (L))</th>
<th>$K_M$ (CHD (ml/min))</th>
<th>$V_{PRE}$ (CHD (L))</th>
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<tr>
<td>1</td>
<td>196 ± 24</td>
<td>5.5 ± 0.9</td>
<td>189 ± 36</td>
<td>5.0 ± 1.1</td>
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<td>2</td>
<td>45 ± 5</td>
<td>5.5 ± 0.5</td>
<td>87 ± 14</td>
<td>10.0 ± 1.5</td>
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<td>3</td>
<td>67 ± 7</td>
<td>7.5 ± 0.7</td>
<td>63 ± 7</td>
<td>12.7 ± 1.7</td>
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<tr>
<td>4</td>
<td>76 ± 11</td>
<td>10.9 ± 1.4</td>
<td>93 ± 14</td>
<td>10.8 ± 1.4</td>
</tr>
<tr>
<td>5</td>
<td>56 ± 7</td>
<td>12.5 ± 1.2</td>
<td>52 ± 3</td>
<td>11.7 ± 0.6</td>
</tr>
<tr>
<td>6</td>
<td>106 ± 19</td>
<td>12.6 ± 2.3</td>
<td>76 ± 15</td>
<td>10.4 ± 2.0</td>
</tr>
<tr>
<td>7</td>
<td>148 ± 41</td>
<td>12.3 ± 3.5</td>
<td>108 ± 13</td>
<td>24.0 ± 3.5</td>
</tr>
<tr>
<td>8</td>
<td>66 ± 11</td>
<td>11.0 ± 1.5</td>
<td>56 ± 5</td>
<td>11.7 ± 1.1</td>
</tr>
<tr>
<td>9</td>
<td>78 ± 5</td>
<td>8.0 ± 0.6</td>
<td>84 ± 6</td>
<td>9.5 ± 0.7</td>
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<tr>
<td>10</td>
<td>68 ± 9</td>
<td>14.5 ± 1.4</td>
<td>96 ± 12</td>
<td>13.9 ± 2.3</td>
</tr>
<tr>
<td>11</td>
<td>132 ± 5</td>
<td>18.8 ± 0.7</td>
<td>98 ± 8</td>
<td>15.7 ± 1.5</td>
</tr>
<tr>
<td>12</td>
<td>104 ± 18</td>
<td>7.2 ± 1.1</td>
<td>102 ± 11</td>
<td>8.8 ± 0.9</td>
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<tr>
<td>13</td>
<td>73 ± 8</td>
<td>11.5 ± 0.9</td>
<td>95 ± 15</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>14</td>
<td>75 ± 11</td>
<td>8.9 ± 1.1</td>
<td>48 ± 8</td>
<td>11.4 ± 1.6</td>
</tr>
<tr>
<td>15</td>
<td>61 ± 7</td>
<td>8.8 ± 1.0</td>
<td>73 ± 11</td>
<td>12.3 ± 1.9</td>
</tr>
<tr>
<td>16</td>
<td>192 ± 38</td>
<td>11.6 ± 2.3</td>
<td>208 ± 23</td>
<td>11.5 ± 1.3</td>
</tr>
<tr>
<td>17</td>
<td>138 ± 19</td>
<td>13.0 ± 1.6</td>
<td>188 ± 29</td>
<td>11.1 ± 1.7</td>
</tr>
<tr>
<td>18</td>
<td>73 ± 11</td>
<td>12.7 ± 1.7</td>
<td>55 ± 6</td>
<td>17.4 ± 1.9</td>
</tr>
<tr>
<td>19</td>
<td>109 ± 55</td>
<td>22.9 ± 9.2</td>
<td>106 ± 15</td>
<td>13.1 ± 1.7</td>
</tr>
<tr>
<td>20</td>
<td>131 ± 19</td>
<td>6.7 ± 1.0</td>
<td>154 ± 14</td>
<td>9.9 ± 1.2</td>
</tr>
<tr>
<td>21</td>
<td>58 ± 5</td>
<td>8.9 ± 0.7</td>
<td>51 ± 5</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>Mean</td>
<td>98</td>
<td>11.0</td>
<td>99</td>
<td>11.9</td>
</tr>
<tr>
<td>SD</td>
<td>44</td>
<td>4.2</td>
<td>47</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Figure 5. Comparison of parameter estimates obtained from short hemodialysis (SHD) and conventional hemodialysis (CHD) treatments. The identity lines represent equality between parameter estimates. $V_{PRE}$, volume of accessible compartment for phosphorus; $K_M$, phosphorus mobilization clearance.

The proposed kinetic model is novel in two major respects compared with other models used to commonly describe solute kinetics during HD. First, the model consists of (I) an accessible compartment with a time-dependent concentration and central distribution volume from which phosphorus is removed by the dialyzer and (2) a second large, undefined volume with constant concentration ($C_{PRE}$) because it is assumed to contain a very large amount of phosphorus. The latter volume, from which phosphorus is continuously mobilized represents all inaccessible phosphorus pools combined. This model structure is consistent with the distribution of phosphorus in the human body where approximately 99% of all phosphorus is stored in bones and soft tissues, and 1% is distributed in the intravascular and interstitial spaces (34). This model structure is also consistent with empirical evidence from the studies by Haas et al. (31) who showed that adding phosphate to the dialysis solution had little influence on the serum phosphorus level before the next HD treatment session. Because all of the time-dependent variables of the kinetic model are within one compartment, we have termed this as a pseudo one-compartment model (Figure 1).

A second novel feature of this model is that the mobilization rate is formulated as a linear function of the difference between the predialytic and the instantaneous plasma phosphorus concentrations. Hence, phosphorus mobilization is minimal at the start of dialysis and increases as the treatment progresses. This formulation explains the rapid decrease of plasma concentration early during dialysis and relatively constant concentration afterwards. Furthermore, the same formulation also explains the postdialytic rebound well. When dialysis is terminated, phosphorus mobilization causes the plasma concentration to quickly recover within the first 60 minutes (Figure 3).

In this regard, this model differs from other compartmental models previously proposed. Sugasaki et al. (21,22) and Gotch et al. (35) proposed modified one-compartment models; the former proposed the incorporation of a time-
dependent phosphorus generation rate, and the latter empirically fit data to an equation derived from a one-compartment model. Neither of these models would predict postdialytic rebound, nor were they compared with data from the postdialytic rebound period. Others have proposed two-compartment models with classical intracellular and extracellular fluid compartments (23,36,37). These models assumed that the volume of the intracellular compartment was (1) comparable to that of the extracellular compartment (i.e. intracellular to extracellular volume ratio of 2:1) and (2) time-dependent. Also, the amount of phosphorus in the intracellular space was assumed to be limited with the concentration decreasing as a function of dialysis duration. The most recent four-compartment model proposed by Spalding et al. (24) is an extension of the classical two-compartment model. Their model is physiologically plausible, but it is too complex for easy clinical application. The data used in those studies were obtained at frequent time intervals (i.e. 30 minutes), which was necessary to make the reported observations and to estimate the large number of patient-specific parameters involved.

We also performed a direct comparison of the conventional two-compartment model and the pseudo one-compartment model to fit these data (not shown). Although those analyses showed that a conventional two-compartment model can provide good fits to these data during SHD and CHD, the two-compartment model cannot predict approximately steady plasma phosphorus levels late in CHD treatments, nor were parameter estimates from the two-compartment model during SHD and CHD treatments in good agreement. Thus, our analyses confirm previous work that applying a conventional two-compartment model to phosphorus kinetics during CHD is problematic (23,24). Although the pseudo one-compartment model does not specifically include a phosphorus generation term, it makes no assumptions about possible phosphorus generation within the inaccessible compartment. This model assumes simply that the rate of phosphorus mobilization from the inaccessible compartment can be approximated by the difference between predialytic and instantaneous plasma phosphorus levels multiplied by \( K_M \). Whether modifications of the pseudo one-compartment model to include additional compartments or phosphorus generation terms can lead to further improvements remains to be demonstrated in future studies.

Although the estimated phosphorus mobilization clearances varied among patients, they were similar for each patient during SHD and CHD sessions. This observation suggests the existence of a unique, patient-specific phosphorus mobilization clearance, independent of HD treatment time. Consequently, extending kinetic model predictions from thrice-weekly conventional to short daily and nocturnal HD therapies may be feasible using a pseudo one-compartment model and patient-specific values of phosphorus mobilization clearance. It should be noted that this study is the first to determine the phosphorus central distribution volume from kinetic data during HD; all previous models have assumed that the volume of the accessible compartment was the same as that for extracellular fluids (22–24,35–37). The predialytic central distribution volume of all patients was estimated to be approximately 12 L, or 15% of body weight, as determined from the CHD sessions, practically equal to extracellular fluid volume (20% of body weight) (38). It should be noted that Ward et al. (39) recently determined the total distribution volume for \( \beta_2 \)-microglobulin kinetically (also expected to be equal to the extracellular fluid volume) and reported values similar to those reported here of 14.3% of body weight. These findings support the typical assumption that the kinetically determined central distribution volume for phosphorus kinetics during HD is the extracellular fluid volume.

This model is relatively simple, and hence, it cannot describe the small rebound in plasma phosphorus concentration that may occur before the end of the HD treatment in some patients. In this study, dialyzer phosphate clearance measured after 60 minutes of treatment was assumed to be constant during the treatments. Although dialyzer phosphate clearance has been shown to decrease during the course of HD treatments, such changes were small (40) and unlikely to have significant effect on the reported results. A key strength of this model is its ability to quantify the phosphorus mobilization characteristics of individual patients. This model strength may also allow a better understanding of physiologically mediated kinetics, such as those regulated by parathyroid hormone or other mediators of mineral metabolism, and lead to more effective treatments for enhancing phosphorus removal during HD and other extracorporeal modalities. The latter would be possible by estimating phosphorus mobilization during HD treatment sessions from intradialytic plasma phosphorus concentrations and optimizing the HD prescription (i.e. dialysis time and frequency) on the basis of model predictions.

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Disclosures

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References


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