ABSTRACT

Hyperphosphatemia is an independent risk factor for mortality and cardiovascular events in patients with chronic kidney disease (CKD). For patients who cannot control their serum phosphate levels adequately with diet, agents that limit gastrointestinal phosphate uptake are indicated. The use of phosphate-binding agents has changed over the years as more is learned about the mechanisms that underlie the clinical effects of hyperphosphatemia and pharmacologic effects of the agents themselves. Calcium-containing oral agents largely replaced aluminum-based products because the latter, although effective, were associated with serious toxicities. A growing body of evidence suggests that calcium-based phosphate binders may increase the calcium load in patients with CKD, accelerating arterial calcification and increasing cardiovascular risk. Sevelamer hydrochloride and lanthanum carbonate are non–calcium-containing phosphate binders currently available for the management of hyperphosphatemia. In addition, several new therapeutic approaches are emerging as the understanding of vascular calcification evolves.


TREATMENT OPTIONS IN THE MANAGEMENT OF PHOSPHATE RETENTION

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Hyperphosphatemia is associated with a range of complications in patients with chronic kidney disease (CKD), such as hyperparathyroidism, osteodystrophy, anemia, and soft-tissue calcification. The need for effective management of serum phosphate levels in end-stage renal disease (ESRD) has long been recognized as a treatment priority, and various management strategies have been used over the years. When controlling phosphate intake by dietary restriction and dialysis are not sufficient, binders that reduce intestinal absorption of phosphate are the mainstay of treatment to control high serum phosphorus. Aluminum-based agents were among the first phosphate-binding agents used. Although they were effective in reducing serum phosphate levels, they also were associated with serious toxicities. Calcium-containing oral preparations replaced the aluminum-based binders and have been used extensively since the late 1980s and early 1990s. However, recent evidence suggests that calcium-binding agents, by contributing an excess calcium load, may exacerbate vascular calcification.

As discussed in the article by Drs Middleton and Malluche earlier in this monograph, both hyperphosphatemia and vascular calcification are associated with increased risk of cardiovascular mortality in patients with ESRD. Thus, alternatives to calcium-containing preparations may be important to reducing the cardiovascular risk in this vulnerable population.

Sevelamer hydrochloride and lanthanum carbonate are calcium- and aluminum-free agents with proven efficacy in the reduction of serum phosphate levels. Preliminary evidence indicates that these agents are not associated with increased vascular calcification. This paper will compare the safety, efficacy, and tolerability profiles of calcium binders, sevelamer, and lanthanum. Data regarding rates of arterial calcification in patients using these agents will be discussed in the
context of current and future options for the management of hyperphosphatemia.

**Phosphate Binders and Bone Disease**

In the 1980s, the increase in parathyroid hormone (PTH) and decrease in calcitriol (1,25-hydroxyvitamin D₃) seen in patients with CKD were associated with mixed uremic osteodystrophy in a high percentage of patients. A smaller proportion of patients presented with more severe forms of renal osteodystrophy, including predominant hyperparathyroid bone disease or aluminum-related osteomalacia. However, by the early 1990s, the incidence of adynamic bone disease and osteomalacia decreased with the virtual elimination of aluminum-based binder use. After 1995, there was an increase in the prevalence of adynamic bone disease without evidence of aluminum toxicity. This increase occurred at the same time as the increased use of calcium-based binders. The increased calcium load resulting from these agents suppressed PTH, particularly when calcium salts were used together with calcitriol supplementation. Distinguishing between adynamic bone disease and hyperparathyroid bone disease is important because the management approach differs depending on the diagnosis. Furthermore, it may be important to balance the calcium turnover present in bones of patients with CKD to minimize the risk of soft-tissue calcification.

**Evolution of Phosphate-Binding Agents**

**Aluminum-Containing Phosphate Binders**

Prior to 1985, aluminum-containing phosphate binders were standard treatment for patients with ESRD, and their efficacy in reducing phosphate absorption was good. However, plasma aluminum levels gradually increase in patients taking aluminum hydroxide, a common formulation. The absorbed aluminum was associated with serious toxicities, including osteomalacia, bone and muscle pain, iron-resistant microcytic anemia, and neurologic abnormalities. As a result of these toxicities, the aluminum-based binders are rarely used as the primary phosphate binder.

**Calcium-Containing Phosphate Binders**

Calcium-based binders became the most frequently used of the phosphate-binding class in the 1980s and 1990s; however, use of these agents may contribute to progressive vascular calcification, indirectly contributing to mortality. Both calcium carbonate and calcium acetate are effective in reducing intestinal phosphorus absorption and in lowering serum phosphate concentrations.

Calcium carbonate is weakly soluble in water and binds phosphate poorly at neutral pH. The gastrointestinal solubility of calcium carbonate preparations can vary, and nondisintegrating tablets have been seen on abdominal radiographs, suggesting minimal intestinal uptake. Calcium acetate is soluble at neutral pH and is able to bind phosphate. Constipation, reported with calcium carbonate, occurs less often with calcium acetate; however, calcium acetate is infrequently tolerated, and patient compliance may be worse than with calcium carbonate. Although lower doses may be required to control hyperphosphatemia, calcium acetate tends to produce hypercalcemia, especially when administered with calcitriol; however, hypercalcemia occurs more often with calcium carbonate than with calcium acetate.

A study designed to determine whether modulating bone turnover affected arterial calcification found that calcium binders may contribute to soft-tissue calcification. Fifty-eight nondiabetic patients with ESRD who were undergoing hemodialysis for at least 1 year were evaluated for the extent of arterial calcifications using ultrasound. Although calcium carbonate was the only phosphate binder being used by the patients at study entry, 33 had taken aluminum hydroxide in the past. The extent of calcification at multiple sites was ranked using a scale ranging from 0 (no calcifications) to 4 (generalized calcifications present in all arterial segments examined). Higher arterial calcification scores were positively correlated with age ($P < .0001$), calcium carbonate phosphate-binder dose ($P < .001$), aluminum-stained bone surfaces ($P < .037$), and decreased osteoblast surfaces ($P < .001$). Hence, excessive calcium load, as well as aluminum, was associated not only with low bone turnover and adynamic bone disease, but also with increased soft-tissue calcification.

**Aluminum- and Calcium-Free Alternatives**

Currently, sevelamer hydrochloride and lanthanum carbonate are the only aluminum- and calcium-free agents available. They are increasingly used in the ESRD population.
**SEVELAMER HYDROCHLORIDE**

Sevelamer hydrochloride is an effective, aluminum- and calcium-free phosphate binder.\(^2\) It also lowers serum low-density lipoprotein (LDL) cholesterol levels, although the clinical significance of this effect has not been demonstrated. Treatment with sevelamer has been shown to stabilize vascular calcification.\(^{15}\) Use of this agent is limited by expense, potential gastrointestinal upset, and requisite high pill burden.\(^{16,17}\)

An open-label, randomized study of 109 adult patients new to hemodialysis compared the effects of sevelamer hydrochloride and calcium phosphate binders on arterial calcification.\(^{18}\) Over the 18-month study duration, both agents decreased serum phosphate levels to a similar extent. However, patients receiving sevelamer hydrochloride had significantly lower mean corrected calcium \((P < .0001)\), higher immunoreactive PTH \((P = .05)\), higher PTH (1-84) \((P = .03)\), lower total cholesterol \((P = .003)\), and lower LDL cholesterol \((P = .0003)\).

A comparison of the effects of phosphate binders on cardiovascular calcification was conducted over 52 weeks in 114 adult patients on hemodialysis. In this open-label study, patients received either sevelamer hydrochloride or calcium carbonate.\(^{19}\) Overall reductions in serum phosphate were similar in the 2 treatment groups. However, patients receiving calcium carbonate had significant increases in coronary artery calcification (median increase, 34%; \(P < .01\)) and aortic calcification (32%; \(P < .01\)) that were not seen in the patients treated with sevelamer hydrochloride (Figure 1). In addition, significantly greater calcification was observed in patients whose serum phosphate levels were above the median value \((P < .01\) for both treatment groups).

As recently reported, patients in this open-label study were followed for the secondary endpoint of all-cause mortality.\(^{20}\) At the end of the 44-month follow-up, 34 deaths were recorded: 11 in the sevelamer hydrochloride group and 23 in the calcium binder group. Coronary artery calcium scores were not significantly different between groups at baseline. After adjustment for age, race, gender, and the presence of diabetes, baseline coronary artery calcium score was a significant predictor of mortality \((P = .002)\). In addition, choice of phosphate binder was also a predictor of mortality. Patients treated with calcium binders had a greater risk of death compared to those treated with sevelamer hydrochloride \((P = .016;\) hazard ratio, 3.1; confidence interval, 1.23–7.61).

**LANTHANUM CARBONATE**

Lanthanum carbonate is an alternative to sevelamer hydrochloride that also is free of calcium and aluminum.\(^{1,21}\) This agent has no known biotransformation and does not have any known local or systemic drug interactions. For example, this agent does not interact with warfarin, metoprolol, or digoxin. Lanthanum carbonate does not cross the blood-brain barrier and thus has a low potential for central nervous system effects.\(^{22}\)

The efficacy of lanthanum carbonate is similar to that of standard therapy in reducing phosphate levels. An open-label, parallel-group active comparator-controlled trial involving 1566 patients evaluated long-term (2-year) safety and tolerability of lanthanum carbonate.\(^{21}\) Patients were included if they were 18 years of age or older and were on maintenance hemodialysis 3 times weekly for at least 2 months immediately prior to the study. Efficacy, having previously been demonstrated, was a secondary endpoint. Lanthanum carbonate treatment was initiated at 750 or 1500 mg/d and titrated according to serum phosphate levels. Patients randomized to standard therapy resumed their prestudy phosphate binder and dosing regimen after the washout period. The serum phosphate levels in both treatment groups decreased during the titration period and remained stable throughout the study.\(^{21}\) Serum phosphate levels were

![Figure 1. Change in Coronary Artery Calcification According to Phosphorus (P) Exposure](image-url)

There were significant changes between patients above and below the median phosphorus value within each group \((P < .01\) for both groups). Reprinted with permission from Braun et al. Clin Nephrol. 2004;62:104-115.\(^{19}\)
adequately controlled (≤5.9 mg/dL) in similar percentages of patients in each treatment group throughout maintenance treatment (Figure 2). At 24 months, 46% of those in the lanthanum carbonate group and 49% of patients in the standard therapy group had controlled levels (P = .5).

Serum calcium levels decreased with lanthanum carbonate treatment during the titration period (Figure 3).21 Levels were consistently lower in the lanthanum carbonate group than with standard therapy throughout the study. Serum calcium levels were not significantly different between groups at baseline. Serum calcium decreased in the lanthanum carbonate group during titration and remained consistently lower than those in the standard therapy group throughout the 2-year study.

Mean PTH levels in patients taking lanthanum carbonate reached the National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommended range (150–300 pg/mL) during titration and remained stable over the study duration. PTH levels in the standard therapy group remained below the recommended range for the entire study period. (Figure 4).21

Serum calcium-phosphorus product (Ca x P) levels decreased during titration and then remained stable in both groups. Analysis of data from an open-label extension of this study and 3 others showed that treatment with lanthanum carbonate maintained control of serum phosphate and Ca x P, and was well tolerated, for up to 6 years of treatment.23 The most commonly reported adverse events were nausea, diarrhea, and flatulence.22 No adverse effects on liver enzyme function were reported during 2 years of follow-up.24

The route of elimination for lanthanum carbonate is via the liver. Adverse effects on liver histology have not been detected in normal and uremic animals given doses of lanthanum carbonate up to 17 times the human clinical dose of 3 g per day. This lack of effect on liver histology is thought to be attributable to the compartmentalization of lanthanum carbonate into lysosomes and transport to the bile for elimination.25

NEW TARGETS FOR THERAPY

Increasing understanding of the molecules that regulate phosphate metabolism as well as those that are involved in arterial calcification provide potential new therapeutic targets to reduce mortality and morbidity associated with CKD. Studies of rare disorders associated with phosphate wasting have led to the discovery of phosphatonin.26 These molecules include fibroblast growth factor (FGF)-23, secreted frizzled-related protein-4, matrix extracellular phosphoglycoprotein, and FGF-7, which decrease renal tubular sodium-dependent phosphate reabsorption, both in vivo and in vitro. These compounds also decrease intestinal phosphate absorption and retention of phosphate by the body.26 However, in contrast to PTH, FGF-23 decreases renal C1α-hydroxylase. Phosphatonin may provide new insight into the molecular controls of phosphate metabolism.
in CKD and have the potential to be useful tools in managing hyperphosphatemia.

Several proteins have been identified that inhibit ectopic calcification in vivo. These include fetuin-A, matrix Gla protein, and osteopontin. These proteins are expressed in atherosclerotic plaques and may provide another therapeutic target to reduce cardiovascular risk resulting from soft-tissue calcification.27

CONCLUSIONS

When patients with CKD develop hyperphosphatemia, this is associated with secondary hyperparathyroidism and elevated Ca x P. Moreover, hyperphosphatemia is an independent risk factor for cardiovascular morbidity and mortality. Traditionally, aluminum-based phosphate binders were used to reduce intestinal absorption of dietary phosphate. However, the toxicity associated with these binders prompted a shift to using calcium-based formulations. Recent evidence suggests that calcium-based phosphate binders contribute to the overall calcium body burden, increasing arterial calcification and cardiovascular risk. Two alternatives to calcium-based phosphate binders, sevelamer hydrochloride and, more recently, lanthanum carbonate, have been developed. Sevelamer hydrochloride and lanthanum carbonate are safe and effective for reducing serum phosphorus levels and may reduce arterial calcification. Greater understanding of the roles of phosphatonin and inhibitors of arterial calcification may provide additional approaches to reducing the impact of soft-tissue calcification in this population.

REFERENCES


