

REVIEW ARTICLE

DRUG THERAPY

Oral Phosphate Binders in Patients with Kidney Failure

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HYPERPHOSPHATEMIA, A NEARLY UNIVERSAL COMPLICATION OF KIDNEY failure, is accompanied by hypocalcemia and low serum levels of vitamin D. Without treatment, these deficiencies usually lead to severe secondary hyperparathyroidism, which in turn leads to painful fractures, brown tumors, and generalized osteopenia. Dietary restriction of phosphate has long been the cornerstone of therapy, but this measure is usually not sufficient to control hyperphosphatemia. As a result, oral phosphate binders are used in over 90% of patients with kidney failure, at an annual cost of approximately \$750 million (in U.S. dollars) worldwide.¹

Historically, treatment with oral phosphate binders was intended to prevent symptomatic secondary hyperparathyroidism. More recently, achieving tighter control of markers associated with abnormal mineral metabolism (e.g., serum phosphate, calcium, and parathyroid hormone levels) has become a specific therapeutic objective.² This therapeutic shift has been driven by several factors: observational data that link disordered mineral metabolism with adverse clinical outcomes; concern about vascular calcification, which is also associated with adverse outcomes and may correlate with exposure to calcium-based phosphate-binding agents; and, perhaps, the availability of new therapeutic agents.³

In this article we review the rationale for treatment with oral phosphate binders, discuss evidence that supports the use of available agents, and suggest an approach for clinical practice.

PATHOPHYSIOLOGY OF HYPERPHOSPHATEMIA IN CHRONIC KIDNEY DISEASE

Inorganic phosphorus is essential for multiple biologic functions such as intracellular signal transduction, the production and function of cell membranes, and energy exchange. Although more than 80% of total body phosphorus is stored in bone and teeth, phosphorus is also found in the intracellular compartment and in serum (primarily in the form of anions such as H_2PO_4^- and HPO_4^{2-} — commonly referred to as phosphate).^{4,5}

In the healthy state, serum phosphate levels are maintained within the physiologic range by regulation of dietary absorption, bone formation and resorption, and renal excretion, as well as by equilibration with intracellular stores. In addition, the skeleton acts as a reservoir, allowing continuous and balanced exchange of phosphate between bone and serum (Fig. 1). A typical Western diet includes 1000 to 1200 mg of dietary phosphate per day from foods such as dairy products, meats, and whole grains, of which approximately 800 mg is ultimately absorbed.⁶ Food

additives that contain phosphorus (e.g., monocalcium phosphate or sodium phosphate) are also important sources of dietary phosphate, potentially accounting for an additional 500 mg per day.⁷

A detailed discussion of phosphate homeostasis is beyond the scope of this review; more comprehensive coverage is provided elsewhere.^{6,8} In people with normal kidney function, renal excretion of excess phosphate is primarily responsible for maintaining phosphate balance. When kidney function is impaired, the excretion of phosphate declines. However, serum phosphate levels do not rise appreciably until the glomerular filtration rate drops below 30 ml per minute per 1.73 m² of body-surface area^{9,10} owing to a compensatory reduction in tubular reabsorption mediated by increased levels of serum parathyroid hormone, fibroblast growth factor 23, and phosphate itself.^{3,11,12} In people with stage IV or V kidney disease, the dietary intake of phosphate exceeds excretion, and without specific treatment, hyperphosphatemia occurs almost universally in those undergoing dialysis despite dietary phosphate restriction (Fig. 1).

Large observational studies have shown a graded association between levels of serum phosphate and all-cause mortality in patients undergoing dialysis. A seminal study in North America showed that patients receiving hemodialysis who had serum phosphate levels above 6.5 mg per deciliter (2.1 mmol per liter) had a 27% higher risk of death than those whose phosphate levels were between 2.4 and 6.5 mg per deciliter (0.8 to 2.1 mmol per liter).¹³ Subsequent analyses showed that an excess risk of death was associated with both high and low levels of serum phosphate (with low levels probably indicating malnutrition). Patients with very high serum phosphate levels (>11 mg per deciliter [3.6 mmol per liter]) had mortality rates that were increased by a factor of approximately 2.5 as compared with patients with much lower phosphate levels (4 to 5 mg per deciliter [1.3 to 1.6 mmol per liter]). More recently, similar findings were reported for populations treated with hemodialysis elsewhere in the United States¹⁴⁻¹⁶ and in other countries¹⁷ and for patients receiving peritoneal dialysis.¹⁸

Several putative mechanisms link elevated serum phosphate levels to increased cardiovascular morbidity and mortality (Fig. 2).^{15,19,20} The

most plausible mechanism concerns the accelerated progression of vascular calcification,²¹ a common complication of dialysis that is associated with adverse clinical outcomes. Vascular calcification is conceptually linked to the positive phosphate balance often seen in kidney failure (Fig. 1). Although some supplemental calcium is required to prevent hypocalcemia, current doses of calcium-based phosphate binders may be excessive, and this excess may contribute to vascular calcification. The putative link among hyperphosphatemia, vascular calcification, and adverse outcomes has been used to justify the need to better control serum phosphate and to minimize oral intake of calcium in patients undergoing dialysis. However, hyperphosphatemia might also identify patients who are less likely to adhere to dietary restrictions (and other aspects of their care) or who receive inadequate dialysis for other reasons, each of which might confer a predisposition to cardiovascular disease (Fig. 2). No randomized trials have compared the merits of intensive and conservative strategies for controlling hyperphosphatemia or shown that any reduction of serum phosphate will reduce mortality; thus, the optimal target level of serum phosphate is unknown.

AVAILABLE PHOSPHATE-BINDING AGENTS

Until the mid-1980s, aluminum was the mainstay of phosphate-binding therapy. Oral aluminum was administered at mealtimes to bind dietary phosphate, but this practice was largely abandoned when its use was linked to systemic aluminum toxicity, manifested as encephalopathy, osteomalacia, and anemia.²²⁻²⁵ Therefore, aluminum-based agents are not discussed further in this review.

The ideal phosphate binder would avidly bind dietary phosphate, have minimal systemic absorption, have few side effects, have a low pill burden, and be inexpensive. Unfortunately, as discussed below, none of the currently available oral phosphate binders meet all these criteria.

CALCIUM-BASED PHOSPHATE BINDERS

Calcium-based phosphate binders, either calcium carbonate or calcium acetate, have been used for decades in patients undergoing dialysis,^{17,26} and

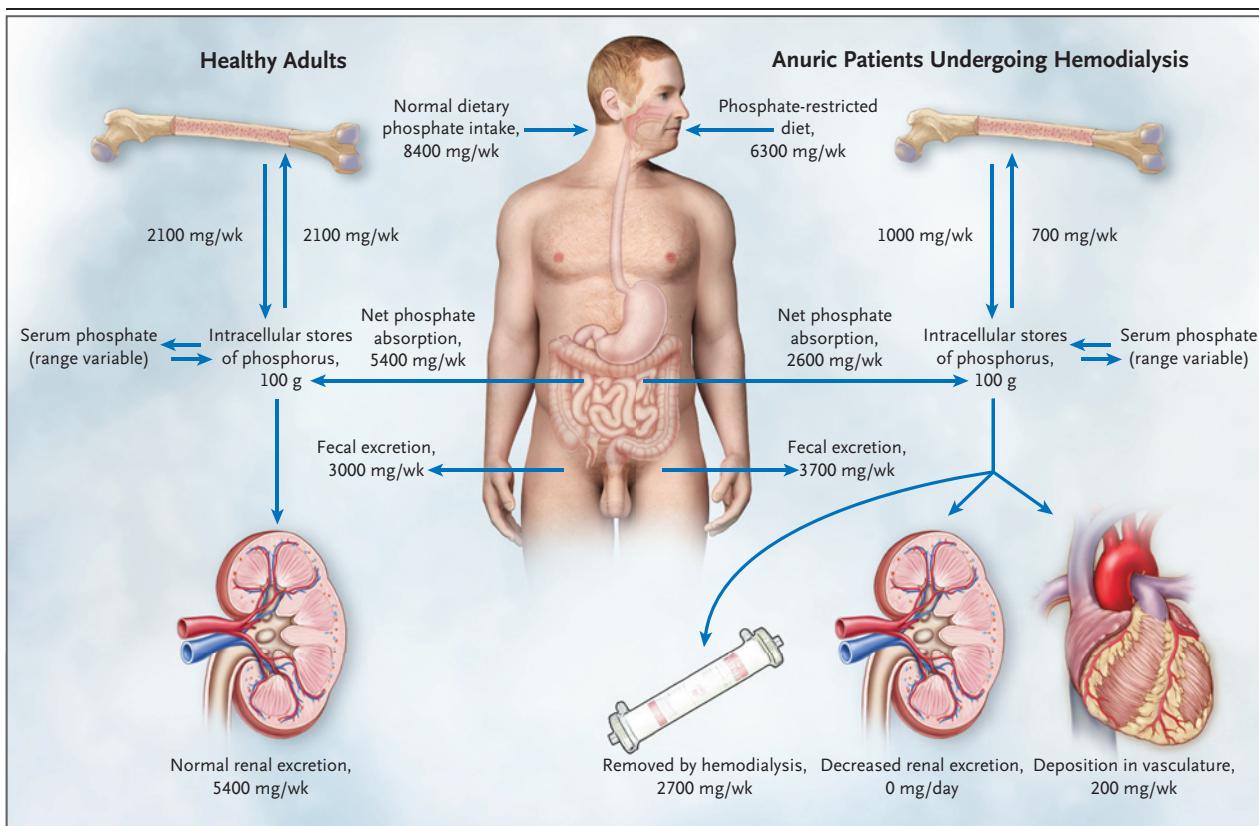


Figure 1. Phosphate Metabolism in Kidney Failure and in Health.

In healthy adults, phosphate intake is matched by phosphate excretion in feces and urine, and the flux of phosphate between the skeleton and the extracellular phosphate pool is approximately the same in both directions. In patients with kidney failure, dietary restriction of phosphate is insufficient to compensate for the decrease in renal phosphate excretion, resulting in a positive phosphate balance. In addition, bone is often resorbed more rapidly than it is formed because of abnormal bone remodeling in kidney failure. Together, these abnormalities may confer a predisposition to vascular calcification, especially when serum phosphate levels are suboptimally controlled. The phosphate values shown are for illustrative purposes only, since these values vary from patient to patient.

the two agents appear to have relatively similar phosphate-binding ability per gram of calcium administered.^{26,27} They are the most commonly used phosphate binders in contemporary practice worldwide.

No placebo-controlled studies have examined the effect of calcium-based agents on clinical end points such as mortality, cardiovascular outcomes or hospitalization, or putative surrogate end points such as vascular calcification.²⁵ It is difficult to synthesize the results of studies comparing calcium carbonate with calcium acetate, since most of these studies used obsolete formulations of the two salts, used doses of calcium that differed between treatment groups, or had small samples. Acknowledging these limitations, a meta-analysis of trials comparing these calcium salts suggested that they were similar in their capacity to lower

serum phosphate, with no evidence of a difference in the risk of hypercalcemia between the two.²⁸

Aside from hypercalcemia, the major adverse events associated with calcium-based agents are gastrointestinal symptoms, although their incidence appears to be lower than that associated with sevelamer (see below)^{29,30} (Table 1). Some studies have suggested that gastrointestinal side effects are less frequent with calcium carbonate than with calcium acetate,⁶⁰⁻⁶⁵ but a recent meta-analysis did not confirm this finding.²⁸

SEVELAMER

Sevelamer is an anion-exchange resin,⁶⁶ first released as sevelamer hydrochloride, and almost all the clinical studies of sevelamer have used this formulation. Given concerns about metabolic acidosis due to the hydrochloride moiety, however, seve-

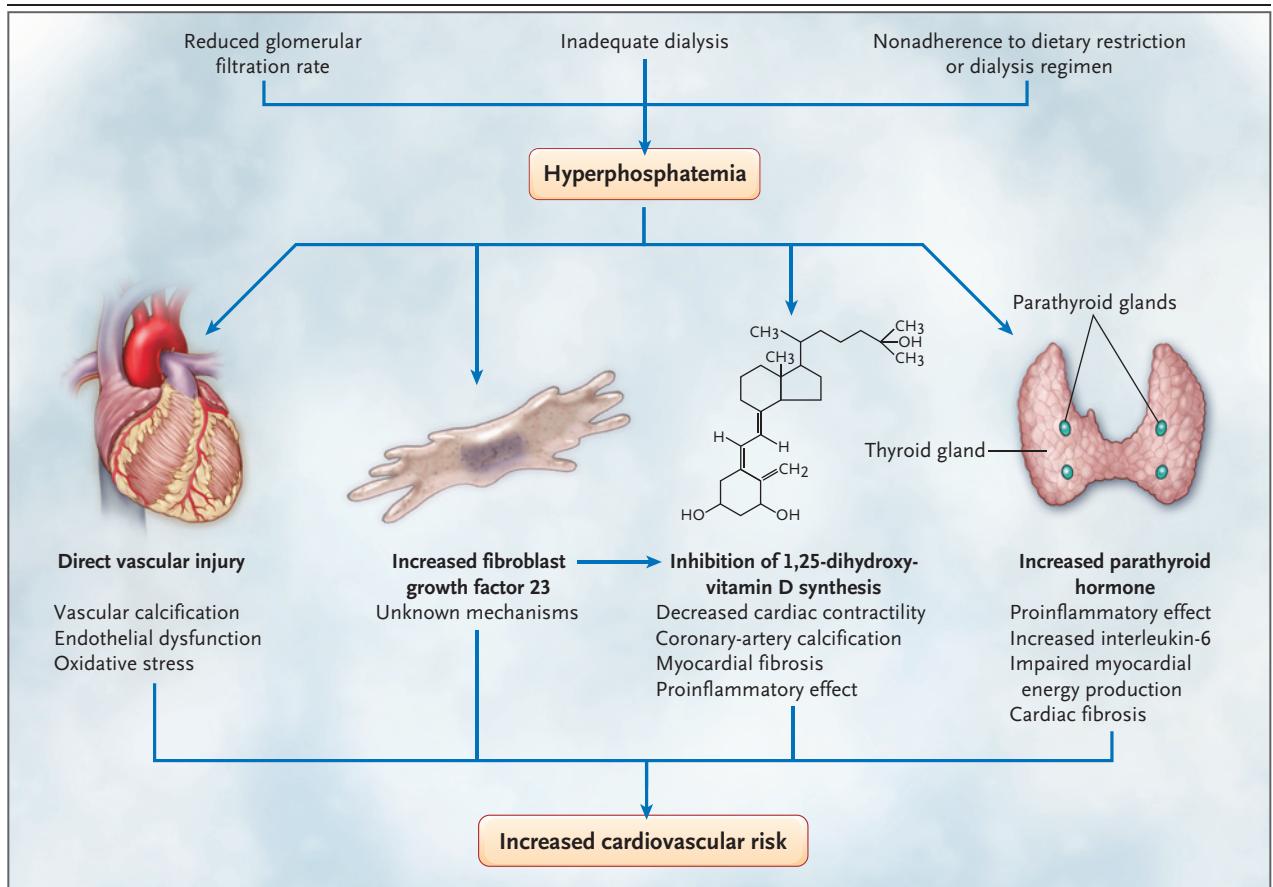


Figure 2. Putative Mechanisms Linking Hyperphosphatemia and Cardiovascular Disease.

Elevated serum phosphate levels are associated with an increased risk of cardiovascular disease among patients with and those without kidney failure, although it is unclear whether phosphate plays a causal role or is simply a marker of a poor outcome. Although much of the research has focused on the role of elevated phosphate levels in vascular calcification, multiple potential mechanisms linking phosphate to cardiovascular disease have been proposed. Hyperphosphatemia may also directly affect vascular health by increasing reactive oxygen species, thereby causing oxidative damage and endothelial dysfunction. Indirectly, hyperphosphatemia increases levels of parathyroid hormone and fibroblast growth factor 23, both of which have been suggested to have direct pathogenic cardiovascular effects. Increased phosphate levels have also been associated with inhibition of 1,25-dihydroxyvitamin D synthesis, which is associated with vascular calcification and myocardial disease. Finally, hyperphosphatemia might also identify patients who are less likely to comply with dietary restrictions (and other aspects of their care), which could confer a predisposition to cardiovascular disease.

lamer is currently approved by the Food and Drug Administration and marketed as sevelamer carbonate, which appears to have a similar effect on phosphate lowering but has been much less extensively studied.^{67,68} Sevelamer use was reported in 17.1% of an international hemodialysis cohort (1996–2008),⁶⁹ although current use in the United States appears to be substantially higher.⁷⁰

Clinical Outcomes

Only one study (Dialysis Clinical Outcomes Revisited [DCOR]) was powered to detect a difference in overall mortality among patients receiving seve-

lamer as compared with those receiving a calcium-based phosphate binder.²⁹ This study enrolled 2103 patients who were undergoing dialysis and were assigned to treatment with either sevelamer hydrochloride or calcium (70% to calcium acetate and 30% to calcium carbonate). The primary analysis revealed no significant difference in mortality between the two groups (hazard ratio with sevelamer, 0.93; 95% confidence interval [CI], 0.79 to 1.10), although secondary analyses suggested a reduction in mortality among patients over 65 years of age who received sevelamer. Secondary analysis of this data set with the use of Medicare claims

Table 1. Common Drug Interactions and Adverse Events with Phosphate Binders.

| Drug* | Interaction | Adverse Effects† |
|--|--|--|
| Sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela) | | Gastrointestinal effects (nausea, vomiting, abdominal pain, bloating, diarrhea, and constipation) in 38% of patients (3.3–67) ^{31–42} Hypercalcemia in 13% of patients (0–22) ^{32,33,37,42} Metabolic acidosis in 34% of patients ^{43,‡} Peritonitis in 11% of patients ³² |
| Lanthanum (Fosrenol) | | Gastrointestinal effects (nausea, vomiting, diarrhea, constipation, and dyspepsia) in 8% of patients (1.4–53) ^{44–51} Hypercalcemia in 6% of patients (0.0–6) ^{45,51,52} Muscular cramping in 7% of patients ⁴⁴ Peripheral edema in 24% of patients ⁵³ Myalgia in 21% of patients ⁵³ Peritonitis in 4% of patients ⁴⁴ |
| Calcium carbonate (Tums, Os-Cal, Caltrate) and calcium acetate (Phoslo, Eliphos) | Interference with absorption of aspirin, digoxin, isoniazid, quinolone, and tetracycline ⁵⁴ | Gastrointestinal effects (nausea, vomiting, diarrhea, constipation, and epigastralgia) in 22% of patients (3.8–49) ^{36,37,42,51,55,56} Hypercalcemia in 10% of patients (12–54) ^{32,33,37,42–44,51,52,57} Peritonitis in 4% of patients ³⁷ Pruritus in 10% of patients ⁵⁶ Xerostomia in 12% of patients ⁵⁶ Muscle cramping in 6% of patients ⁴⁴ |
| Magnesium hydroxide (Milk of Magnesia) and magnesium carbonate (Gaviscon§) | Impaired absorption of oral iron ⁵⁸ | Gastrointestinal effects (diarrhea and constipation) in 20% of patients (4–35) ^{55,59} Hypermagnesemia in 4% of patients ⁵⁹ |

* Trade names may vary among countries; the examples given here are for illustrative purposes only.

† Where multiple studies are cited, the percentages are median values, with ranges given in parentheses.

‡ The mean serum bicarbonate level is 1.43 mmol per liter higher with sevelamer carbonate than with sevelamer hydrochloride.

§ Some preparations of Gaviscon contain aluminum rather than magnesium carbonate.

data showed a reduced risk of all-cause hospitalization among patients receiving sevelamer (relative risk, 0.90; 95% CI, 0.82 to 0.99)³¹; however, there was no significant difference in the risk of hospitalization for cardiovascular causes (the putative mechanism for a benefit from sevelamer).

One small study, involving 148 patients who were starting treatment with dialysis, suggested higher adjusted mortality among patients receiving calcium carbonate or acetate than among those receiving sevelamer hydrochloride (hazard ratio, 3.1; $P=0.02$),⁷¹ although unadjusted mortality did not differ significantly between the two groups.⁷² A meta-analysis of the results of five randomized trials (involving a total of 2429 participants) showed no significant difference in mortality among those treated with sevelamer hydrochloride as compared with those treated with calcium-based agents (risk difference, –2%; 95% CI, –6 to 2),³⁰ and these findings were confirmed by two more recent meta-analyses that included results from an additional five small trials.^{28,73} No randomized trials have compared health-related quality of life, occurrence of cardiovascular events, or presence of symptomatic bone disease between

patients receiving sevelamer and those receiving calcium-based preparations or other agents. Thus, overall, there is no conclusive evidence that treatment with sevelamer improves clinically relevant end points when it is compared with other currently available phosphate binders.

Vascular Calcification and Histologic Features of Bone

In seven trials of sevelamer hydrochloride in patients undergoing dialysis, progression of vascular calcification was considered as an outcome, and the results were variable.^{32,33,74–78} In one study, differences in the progression of vascular calcification were noted only for the subgroup of patients who had baseline calcifications³³; in another study, differences in calcification were found only after 18 months of follow-up.³² Both these studies were carried out with open-label sevelamer, and less than 75% of the participants underwent follow-up computed tomographic scanning to assess progression of vascular calcification. Results of other studies have been contradictory; some suggested that sevelamer did slow the progression of vascular calcification,^{74,77} but others did not

find this to be so.^{75,79} A pooled estimate from a recent meta-analysis that included five of seven available studies suggested that the effect of sevelamer on vascular calcification was not significant.⁷³ Overall, the available studies do not indicate that sevelamer improves the histologic features or turnover of bone,⁷⁹⁻⁸¹ as compared with calcium. Given the inconsistencies among these study results, larger studies with documented, a priori analysis plans will be needed to determine the effect, if any, of sevelamer on vascular calcification or bone health.

Effect on Biochemical Markers

A recent meta-analysis of trials comparing sevelamer and calcium-based phosphate binders (involving a total of 3012 participants with advanced kidney disease) reported levels of serum phosphate, serum calcium, and intact parathyroid hormone.²⁸ Although pooled analyses suggested slightly lower serum phosphate levels in patients assigned to calcium-based binders, the largest clinical trial, which involved 2103 participants, showed equivalent phosphate control.²⁹ Pooled analyses showed that the serum calcium level was significantly lower, by 0.09 mmol per liter (95% CI, -0.11 to -0.06), and that the relative risk of hypercalcemia was 0.47 (95% CI, 0.36 to 0.62) for sevelamer recipients as compared with calcium recipients.²⁸ Although intact parathyroid hormone levels were not reported in the largest clinical trial, the pooled results from smaller trials suggest that these levels were higher among patients assigned to sevelamer.²⁸

Safety

A meta-analysis of three trials involving a total of 2185 patients undergoing dialysis compared the risk of serious adverse events among recipients of sevelamer and recipients of calcium-based binders.³⁰ The pooled risk difference was of borderline significance (13% lower in the group of patients who received calcium-based binders; 95% CI, -2% higher to 29% lower), and all three trials suggested less overall toxicity with calcium-based binders.³⁰ This is consistent with the results of the largest trial, in which 7.7% of sevelamer recipients and 4.8% of calcium recipients were withdrawn from the studies owing to adverse events.²⁹ Sevelamer hydrochloride and sevelamer carbonate appear to have similar gastrointestinal safety profiles,⁶⁷ although sevelamer has been associated

with a slightly higher serum bicarbonate level (1.43 mmol per liter).⁶⁸

LANTHANUM

Lanthanum carbonate is a nonaluminum, noncalcium phosphate-binding agent. Four short-term trials have compared lanthanum with placebo,^{57,82-84} and three trials have compared lanthanum with calcium-based binders.^{44,85,86} Four of the trials were double-blind, placebo-controlled studies that lasted from 4 to 6 weeks, two were open-label studies that lasted up to 1 year, and one was an open-label comparison of lanthanum with standard therapy (largely calcium-based phosphate binders) that lasted for 2 years.⁸⁵ Withdrawal rates in the longer-term trials were high,^{44,85,86} with rates of 71% among lanthanum recipients in the largest trial,⁸⁵ including 14% and 16% of the recipients who were withdrawn because of adverse events and those who withdrew consent, respectively.

Clinical End Points

No good-quality studies have been powered to examine the effect of lanthanum on clinical end points. None of the trials cited showed significant differences between lanthanum and calcium with respect to the rate of bone fracture, quality of life, or cardiovascular complications.⁸⁷

Vascular Calcification and Histologic Features of Bone

No studies have assessed the effect of lanthanum on vascular calcification. Three small trials have compared the effects of lanthanum and calcium carbonate on bone histologic features.^{52,86,88} Biopsies showed overall better bone turnover among the patients receiving lanthanum than among those receiving calcium, and after 1 year, more of the patients who received calcium were found to have histologic features of adynamic bone disease.^{86,88} However, the clinical importance of these histologic differences between treatment groups is unclear.²⁵

Biochemical End Points

Lanthanum and calcium-based phosphate binders appear to be similarly effective in reducing serum phosphate concentrations in patients with end-stage renal disease.^{85,86} However, methodologic flaws in the largest clinical trials (including lack of blinding and substantial loss to follow-up) limit interpretation of the results.⁸⁵ In the largest

Table 2. Effects of Phosphate Binders on Clinical Outcomes, Vascular Calcification, and Relevant Biochemical End Points.*

| Drug† | Daily Dose (pill burden) | Advantages | Disadvantages | Effect on Mortality |
|--|---------------------------------------|---|---|--|
| Calcium carbonate (Tums, Os-Cal, Caltrate) | 500–1250 mg (3–6 tablets) | Effective, inexpensive | May contribute to hypercalcemia, promote vascular calcification, or both | Unknown |
| Calcium acetate (Phoslo, Eliphos) | 667 mg (6 to 12 caplets) | Effective, inexpensive | May contribute to hypercalcemia, promote vascular calcification, or both | Unknown |
| Magnesium hydroxide (Milk of Magnesia) | 311 mg (1 to 6 tablets) | Effective, inexpensive | Potential for respiratory depression with hypermagnesemia; diarrhea is common | Unknown |
| Magnesium carbonate (Gaviscon‡) | 63 mg (2 to 6 tablets) | Effective, inexpensive | Potential for respiratory depression with hypermagnesemia; diarrhea is common | Unknown |
| Sevelamer hydrochloride (Renvela) | 800 mg (6 to 12 caplets) | Effective, does not contain calcium, reduces low-density lipoprotein cholesterol | Adverse gastrointestinal effects; higher cost | No difference in overall or cardiovascular survival with sevelamer vs. calcium-based phosphate binders |
| Sevelamer carbonate (Renvela§) | 800 mg (6 to 12 caplets) | Same active substance as sevelamer hydrochloride but associated with a lower risk of metabolic acidosis | Gastrointestinal adverse effects; high cost | Unknown but presumably similar to sevelamer hydrochloride |
| Lanthanum (Fosrenol) | 250–1000 mg (3 to 6 chewable tablets) | Effective, does not contain calcium | Potential for accumulation in bone and other tissues; high cost | Unknown |

* Costs are based on average dose requirements for patients with end-stage renal disease, as recommended in the product monographs. Doses are consistent with those reported in the largest clinical trials.^{33,73,81,85} The costs shown are average wholesale prices and were obtained from the Thomson Healthcare 2009 Red Book⁹⁵ (except for the costs of magnesium hydroxide and magnesium carbonate, which were obtained from McKesson Canada pharmaceutical data). Purchasers such as Medicare may receive substantial discounts on average wholesale prices. To convert the values for phosphate to millimoles per liter, multiply by 0.3229. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† Trade names may vary among countries; the examples given here are for illustrative purposes only.

‡ Some preparation of Gaviscon contain aluminum rather than magnesium carbonate.

§ Sevelamer carbonate has replaced sevelamer hydrochloride because of concerns about metabolic acidosis due to the hydrochloride moiety.

trial, the proportion of patients who had documented episodes of hypercalcemia was significantly smaller among the patients receiving lanthanum (4.3%) than among those receiving standard care — in most cases, calcium-based binders (8.4%).⁸⁵

Safety

In seven of the eight trials that reported such information, withdrawals due to adverse events were more frequent among the lanthanum-treated patients than among those who received other phosphate binders (usually calcium-based).⁸⁷ For

instance, in the largest clinical trial,⁸⁵ 14% of lanthanum recipients were withdrawn owing to adverse events, as compared with 4% of those who received other binders. Although lanthanum is poorly absorbed, bone-biopsy specimens from patients who had been treated with lanthanum for up to 4.5 years showed rising levels of lanthanum over time.⁸⁷ The results of open-label extension studies of randomized, controlled trials suggest that the incidence of adverse events is stable over time, but few patients receiving lanthanum have been followed for longer than 2 years.⁴⁵

| Effect on Coronary-Artery Calcification | Effects on Calcium and Phosphate | Approximate Annual Cost* <i>U.S. dollars</i> | Comments |
|--|--|---|--|
| Unknown | Serum phosphate declines by 0.9 mg per deciliter on average, whereas serum calcium increases by 0.5 mg per deciliter on average, in comparison with no treatment | 100–200 | Reduction in serum phosphate and elevation in serum calcium are dose-dependent |
| Unknown | Reduction in serum phosphate is slightly greater than with calcium carbonate, but serum calcium levels are similar | 1,000–2,000 | Phosphate control appears to be superior and hypercalcemia appears to be less frequent with calcium acetate (than with calcium carbonate), although the studies demonstrating these findings had limitations |
| Unknown | Phosphate-lowering capacity appears to be similar to that of calcium-based agents; often used as add-on therapy with calcium-based agents | 120 | Data are insufficient to recommend one magnesium salt over another |
| Unknown | Phosphate-lowering capacity appears to be similar to that of calcium-based agents; often used as add-on therapy with calcium-based agents | 120 | Data are insufficient to recommend one magnesium salt over another |
| Trend toward less progression of calcification with sevelamer as compared with calcium-based binders | Serum phosphate is lower with calcium-based phosphate binders; serum calcium is lower with sevelamer | 4,400–8,800 | Conclusions regarding vascular calcification cannot be drawn, given methodologic limitations of the studies that assessed this outcome |
| Unknown but presumably similar to that of sevelamer hydrochloride | Effects are similar to those of sevelamer hydrochloride | 5,500–11,000 | As with sevelamer hydrochloride, serum bicarbonate and chloride levels and markers of vitamins D, E, and K and folic acid status should be monitored during therapy |
| Unknown | Effects are similar to those of calcium-based phosphate binders, but with fewer episodes of hypercalcemia | 7,000–14,000 | |

MAGNESIUM-BASED PHOSPHATE BINDERS

Although oral magnesium has been used as a phosphate binder for many years, relatively few data are available concerning its efficacy and safety. Serum magnesium levels are higher in patients undergoing dialysis than in persons with normal kidney function, and hypermagnesemia with respiratory arrest has been reported after excessive oral magnesium ingestion in such patients. Accordingly, most contemporary hemodialysis programs severely restrict or avoid the administration of medications that contain magnesium.

No studies evaluating magnesium-based binders have measured clinical end points or bone histologic features. In a randomized trial of 46 patients receiving hemodialysis, monotherapy with magnesium carbonate, in conjunction with a lower magnesium concentration in the dialysate (0.3 mmol per liter), was compared with calcium

carbonate.⁵⁹ Serum phosphate levels and the risk of adverse events were similar in the two groups during this 6-month study, although calcium recipients had lower levels of parathyroid hormone. Similar findings were reported when magnesium-based agents were used together with calcium-based binders,⁶² although in this study, hypercalcemia was less common in the combination-therapy group. Taken together, the results of these studies and others^{55,89-93} suggest that magnesium binders may have theoretical advantages over calcium-based binders that are similar to the advantages of other non-calcium-based binders, including a reduced calcium load. However, all these studies were small and of short duration. In the absence of long-term data on safety and efficacy, oral magnesium cannot currently be recommended for first-line use as a phosphate binder.

SUMMARY OF CLINICAL DATA

Clinical experience indicates that oral phosphate binders are required to prevent disabling bone disease in patients undergoing hemodialysis, and observational data suggest that such treatment reduces mortality,⁹⁴ yet information to guide the optimal use of these agents is lacking. Most randomized trials have important methodologic limitations such as incomplete reporting, lack of patient blinding, and substantial loss to follow-up (exceeding 50% in one of the key trials^{29,30}). Furthermore, few trials have been placebo-controlled or have addressed clinically relevant outcomes. Rather, the majority of studies have measured putative surrogate outcomes for cardiovascular disease (e.g., calcium-phosphate product or vascular calcification) and survival in end-stage renal disease (e.g., serum phosphate levels).³³ Although plausible rationales link these unvalidated surrogate outcomes with the risk of cardiovascular events, no randomized trials have shown that selecting a particular phosphate binder will reduce the risk of clinically relevant outcomes. On the other hand, the few placebo-controlled trials that have been reported have shown that all currently available agents are associated with sustained reductions in serum phosphate levels, thus presumably reducing the risk of severe hyperparathyroidism.

COST AND COST-EFFECTIVENESS OF AVAILABLE AGENTS

On the basis of the usual doses used,^{33,75} the cost of treatment with calcium acetate — \$1,500 to \$2,000 (in U.S. dollars) per year — is substantially higher than the cost of calcium carbonate or magnesium-based binders (Table 2). Sevelamer and lanthanum are both substantially more costly than any of these older agents, with annual costs, based on average wholesale prices, ranging from \$4,400 to \$14,000 (in U.S. dollars), depending on the dose (Table 2). Although purchasers such as Medicare may receive major discounts, the costs of sevelamer and lanthanum remain substantially higher than the costs of other available agents. One cost-effectiveness analysis based on findings of the DCOR study estimated a cost per quality-adjusted life-year gained of about \$150,000 (in Canadian dollars).⁹⁶ Better estimates of the true cost-effectiveness of these agents will require more reliable estimates of clinical effectiveness.

SUGGESTIONS FOR MANAGEMENT OF HYPERPHOSPHATEMIA

Dietary phosphate restriction effectively reduces serum phosphate levels and should be encouraged for all patients with end-stage renal disease. Although the optimal method of facilitating adherence to a phosphate-restricted diet is unknown, more frequent patient contact with renal dietitians may be beneficial, at least initially.⁹⁷ In addition, specific counseling about the need to avoid phosphate-containing food additives leads to a substantial reduction in serum phosphate, as compared with the usual education about foods that are naturally high in phosphate.⁹⁸ Even with careful dietary modification, most patients undergoing dialysis will continue to require oral phosphate binders. Given the potential dangers of using unvalidated surrogate end points to support the treatment choice,⁹⁹ the selection of a particular phosphate binder cannot be justified solely on the basis of its effects on hyperphosphatemia or vascular calcification. Rather, we consider calcium-based agents to be the first-line phosphate binders for patients undergoing dialysis, since these preparations remain the least expensive and best tolerated option for the treatment of hyperphosphatemia. Although the optimal starting dose has not been studied, many clinicians initially prescribe 200 mg of elemental calcium with each meal for these patients.

Sevelamer and lanthanum are promising, but their superiority to calcium-containing agents has not been proved. Furthermore, they are expensive and are associated with more adverse events. In the absence of their proven clinical benefit as compared with calcium-based agents, in our view sevelamer and lanthanum cannot be recommended as initial therapy. Although the use of these drugs to supplement or replace calcium-based agents in patients with severe vascular calcification has been advocated,²⁵ this strategy has not been tested in clinical trials. For patients in whom phosphate levels cannot be controlled with calcium-based agents alone (especially patients with hypercalcemia), short courses of magnesium-based binders are an inexpensive alternative. However, careful monitoring of serum magnesium levels is required (perhaps in conjunction with a lower magnesium concentration in the dialysate), and the long-term safety and efficacy of this approach are unknown. Some physicians may prefer to use sevelamer or lanthanum despite their higher cost.

Since the ideal target level of serum phosphate is not known, the initial goal of therapy should be to reduce the level until it approaches the normal range,²⁵ recognizing that normophosphatemia will be unattainable for most patients. Whether other agents should be added to improve phosphate control should be considered in light of the severity of concomitant hyperparathyroidism, the patient's pill burden, the risk of adverse events, the cost of additional treatment, and the absence of definitive evidence of a benefit of tight phosphate control.

AGENTS UNDER DEVELOPMENT

A number of new calcium-free phosphate binders are under study. For example, magnesium iron hydroxycarbonate (fermagate) in a dose of 1 g given 3 times a day before meals was associated with reduced serum phosphate levels, but a higher dose (6 g per day) was associated with adverse gastrointestinal events.¹⁰⁰ MCI-196 (colestilan), a novel nonmetallic anion-exchange resin (similar to sevelamer), was associated with reductions in phosphate of approximately 0.2 mmol per liter as compared with placebo, but the longest trial in humans to date has been 3 weeks.¹⁰¹ Treatment with niacin and nicotinamide, as compared with placebo, is associated with a significant reduction in serum phosphate levels, possibly through direct inhibition of the sodium-dependent phosphate cotransporter Na-Pi-2b in the gastrointestinal tract.^{102,103} All these newer agents can be given once daily and do not need to be taken with meals. MCI-96, niacin, and nicotinamide also lower serum cholesterol levels^{101,102} and may reduce levels of triglyceride-rich lipoproteins, although the clinical importance of these effects is unclear.

Patients with advanced kidney disease often have markedly elevated salivary phosphate concentration, which is independent of food content. Since phosphate in swallowed saliva can be absorbed in the gastrointestinal tract, it may be a target for phosphate binders. A recent study showed that chewing gum containing a novel chitosan compound was effective in lowering serum phosphate levels in parallel with reductions in salivary phosphate levels.¹⁰⁴

To date, no information is available as to whether any of these newer phosphate binders affect bone histologic features, vascular calcification, hospitalizations, or mortality. Therefore, larger,

double-blind studies with longer follow-up and clinical outcomes as end points are required before these agents can be recommended for clinical use.

EVOLVING AND FUTURE RESEARCH

Preventing severe hyperphosphatemia remains an important objective in the care of patients with kidney failure. However, achieving tight control of serum phosphate is difficult, and available data do not indicate that lower levels of serum phosphate necessarily lead to better outcomes. The optimal method for controlling serum phosphate in patients undergoing dialysis is unknown and may involve combinations of conventional and novel phosphate binders as well as complementary strategies such as dietary modification⁹⁹ and enhancement of phosphate clearance through longer dialysis sessions¹⁰⁵ or larger dialysis membranes.¹⁰⁶ Further study to determine whether sevelamer or lanthanum improves clinically relevant outcomes (perhaps in patients with, or at high risk for, vascular calcification) should be a high priority for researchers, as should an adequately powered trial to evaluate the safety and benefits of add-on treatment with magnesium carbonate.

A greater understanding of the role of phosphatonins in regulating phosphate metabolism may eventually offer alternative approaches to the prevention, treatment, and monitoring of metabolic bone disease. Fibroblast growth factor 23 (FGF-23)¹⁰⁷ is one of several recently described proteins that appear to play a key role in phosphate and 1,25-dihydroxyvitamin D homeostasis in the healthy state but that may be pathogenic in kidney failure.¹⁰⁸ Such molecules may ultimately prove suitable for monitoring the effectiveness of phosphate-binding therapy or might constitute novel therapeutic targets.⁸ Studies are also needed to determine whether changes in coronary-artery calcification predict cardiovascular events and whether normalization of serum phosphate levels, as compared with less stringent control measures, improves outcomes.

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