A new era in phosphate binder therapy: What are the options?

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Dietary restriction of phosphorus and current dialysis prescription are unable to maintain phosphorus levels within the recommended range (2.7–5.5 mg/dl) in patients with advanced chronic kidney disease (CKD). Therefore, phosphate binders that limit the absorption of dietary phosphorus are commonly prescribed for this patient group. The first phosphate binders were introduced more than 30 years ago and included aluminum salts; however, although effective binders, the use of these agents was subsequently restricted because of concerns over aluminum accumulation in the central nervous system, bone, and hematopoietic cells. In subsequent years, calcium salts, namely calcium carbonate and calcium acetate, became the most widely used phosphate binders; however, increasing evidence now suggests that prolonged use of these agents increases the total body calcium load, induces adynamic bone, and potentially increases the risk of cardiovascular and soft tissue calcification. Sevelamer is the first phosphate-binding agent that is non-absorbed, calcium-free, and metal-free. To date, this agent has been shown to effectively control serum phosphorus levels in patients with CKD. It may also attenuate coronary and aortic calcification and has a number of other beneficial effects on lipid metabolism and inflammation among others. Lanthanum carbonate is another new agent that is reported to provide similar phosphate control to calcium-based phosphate binders but concerns that the long-term administration of such compound may lead to tissue accumulation may limit its use.

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Phosphate-binding agents are indicated to the vast majority of adult and pediatric patients undergoing current standard dialysis regimens.[1] Reducing the daily dietary load of phosphorus by restricting the intake of foods with high phosphorus content cannot be undertaken without severely compromising protein intake. Furthermore, long-term compliance with a restricted diet is generally poor. In addition, current dialysis prescription is unable to maintain normal phosphorus balance if an adequate protein intake is given.[1,2] Prolonged nocturnal dialysis has been shown to achieve better control of phosphorus compared to short daily dialysis and the use of phosphate binders may not be required. In some instances, phosphate should be added to the dialysate solution.[3,4] However, such dialytic modality is not yet widely accepted. Therefore, because of these limitations, the majority of patients with advanced chronic kidney disease (CKD) require treatment with phosphate binders to limit the absorption of dietary phosphorus and to maintain serum phosphorus levels within the normal physiological range.

Since their first introduction more than 30 years ago, the use of phosphate-binding agents has progressed from aluminum-based binders in the 1970s to the widely used calcium-based agents. Recent years have seen the introduction of newer agents such as sevelamer hydrochloride and lanthanum carbonate (Table 1). Although all the phosphate binders are effective in controlling serum phosphorus levels, the older agents, such as the aluminum- and calcium-based binders can be associated with serious adverse effects. The use of aluminum leads to accumulation and in some cases toxicity, whereas the use of calcium-based binders is associated with the induction of adynamic bone disease, increments in serum calcium levels, more frequent episodes of hypercalcemia, and the development of vascular calcifications. The development of calcium-free-metal-free phosphate binders such as sevelamer opens a new approach to the treatment of the renal bone diseases and the process of vascular calcifications. Lanthanum carbonate, a newly approved calcium-free-metal-based phosphate binder, is effective without inducing changes in serum calcium, but there are concerns with long-term administration. The aim of this review is to provide an update on the advantages and disadvantages of the different available phosphate binders in patients treated with maintenance dialysis.

Table 1 | Comparison of the various phosphate-binding agents

Compound	% calcium absorbed (estimate)	Phosphorus (mg) bound per mg Ca^{2+} absorbed	Estimate of potential binding power	Advantages	Adverse effects
Calcium carbonate	~20–30%[a]	~1 mg P bound per 8 mg Ca absorbed[a]	~39 mg P bound per 1 g $CaCO_3$[d]	Inexpensive, wide variety of products/availability	Hypercalcemia, extra-skeletal calcification, GI side effects, constipation
Calcium acetate	With meals: 21±1%; between meals: 40±4%[b]	~1.04 mg P bound per mg Ca absorbed;[c] 1 mg P bound per 2.9 mg Ca absorbed[a]	~45 mg P bound per 1 g calcium acetate[b]	Less calcium absorption than $CaCO_3$; P binding similar to $Al(OH)_3$[c]	Hypercalcemia, extra-skeletal calcification, GI side effects
Magnesium carbonate/calcium carbonate	Contains 450/300 mg calcium acetate	~1 mg P bound per 2.3 mg Ca absorbed	N/A	Potential to minimize calcium load	Hypermagnesemia; no long-term studies of efficacy and safety
Aluminium hydroxide	None	N/A	Liquid: mean binding 22.3 mg P per 5 ml; tablet/cap mean binding 15.3 mg P per tablet/cap[e]	Effective phosphate binding	Constipation/fecal impaction, bone mineral defects, aluminium toxicity, chalky taste, GI distress, nausea, and vomiting
Aluminium carbonate	None	N/A	Same as above	Same as above	Same as above
Sevelamer hydrochloride	None	N/A	Unknown[f]	Non-calcium, non-aluminium. Effective phosphate binder	GI side effects

GI, gastrointestinal; N/A, not available.
Adapted with permission from the National Kidney Foundation.
[a]Emmett *et al.* 1991.
[b]Schiller *et al.* 1989.
[c]Sheikh *et al.* 1989.
[d]Slatopolsky *et al.* 1986.
[e]Balasa *et al.* 1987.
[f]Rosenbaum *et al.* 1997.

SELECTING A PHOSPHATE BINDER

Aluminum-based binders

Until the mid-1980s, the aluminum-containing phosphate binder, aluminum hydroxide, and to a lesser extent aluminum carbonate, constituted the mainstay of treatment for hyperphosphatemia in patients with CKD.[2,5] However, although aluminum salts are highly effective as phosphate binders, it is now recognized that chronic administration of these compounds leads to significant accumulation of aluminum in the central nervous system, bone and hematopoietic cells, and the development of severe toxic effects including encephalopathy, osteomalacia, myopathy, and microcytic anemia.[5,6] Patients with CKD treated with aluminum salts are particularly susceptible to the effects of cumulative ingestion of aluminum because plasma protein binding prevents the removal of high concentrations of aluminum by dialysis.[7] Furthermore, when recommended 'safe' doses of aluminum hydroxide were prospectively compared to calcium-based binders, Salusky *et al.*[8] demonstrated that, aluminum hydroxide was less effective than calcium carbonate as a phosphate binder, and plasma aluminum levels increased over time and were associated with an increased aluminum body burden. One patient actually developed aluminum bone disease in this study. Thus, if prescribed, aluminum should be used only for 4–8 weeks.[9] Moreover, care should be taken to avoid concomitant use of sodium citrate or calcium citrate, which markedly enhance gastrointestinal absorption of aluminum.[10,11]

Calcium-based binders

Of the available calcium-based binders, calcium carbonate and calcium acetate are the most widely used, significantly lowering serum phosphorus levels.[12–14] In general, calcium salts are less effective phosphate binders than aluminum salts; this is because the dissolution of ionized calcium carbonate, the most widely used calcium salt, is very pH dependent and is maximal below pH 5 which is in direct contrast to the higher pH necessary for the binding of calcium to phosphorus.[2,15] Although calcium-based phosphate binders are still commonly used, increasing evidence suggests that intestinal absorption of the large doses of calcium required to adequately control phosphorus levels contributes to continued calcium overload, positive calcium balance, increases in serum calcium levels, more episodes of hypercalcemia, adynamic bone disease, and diminished bone buffer capacity.[14,16,17] This increase in total body calcium load potentially increases the risk of cardiovascular and other soft tissue calcification.[18–21]

In a study of young adults with CKD stage 5, daily calcium intake from calcium-containing phosphate binders in patients with coronary artery calcification scores determined by electron beam computed tomography, was found to be