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A comparison of clinically useful phosphorus binders for patients with chronic kidney failure

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A comparison of clinically useful phosphorus binders for patients with chronic kidney failure. Over the past 30 years it has become apparent that hyperphosphatemia plays a major causative role across the entire spectrum of morbidity associated with advancing kidney dysfunction and failure. A large fraction (60% to 70%) of dietary phosphorus is absorbed and normally excreted by the kidneys. Ideally, as kidney function deteriorates, the net quantity of phosphorus absorbed from the GI tract should be proportionally reduced to match the decrease in kidney function. After initiation of chronic dialysis therapy, the absorbed phosphorus load should match the amount of phosphorus removed via dialysis plus any excreted by residual kidney function. Because it is very difficult to reduce dietary phosphorus to these levels, a variety of oral phosphorus binders have been employed. Currently available binders include alkaline aluminum, magnesium, and calcium salts (primarily calcium carbonate and calcium acetate), various iron salts, and the binding resin sevelamer hydrochloride. Lanthanum carbonate is the newest agent and will probably be released shortly. This review compares the theoretic and in vitro chemistry of these drugs with in vivo data obtained in both normal patients, and in patients with kidney failure. The clinical potency and potential toxicity of the binding agents are compared, and optimal drug administration strategies are also reviewed.

The average daily phosphorous intake of North American or European adults is about 1000 mg in women and 1500 mg in men [1]. Between 60% and 70% of ingested phosphorus is absorbed in the small bowel (primarily in the duodenum and jejunum). In normal adults, average daily urinary phosphorus excretion equals the net phosphorus absorption by the gastrointestinal (GI) tract. Phosphorus balance is positive in growing children and pregnant women due to increases in body, and or fetal, mass.

The kidney normally filters large amounts of inorganic phosphorus and then reabsorbs >90% of this load in the tubules, so that excretion is less than 10% of the filtered load. Early kidney dysfunction and reduced glomerular filtration decreases the filtered load of phosphorus, but tubule reabsorption of phosphorus also decreases so that urinary phosphorus excretion continues to match GI absorption. This compensating reaction is largely because of secondary hyperparathyroidism–increased parathyroid hormone (PTH) levels marked reduce renal tubule phosphorus reabsorption. Equality between phosphorus input and output, with only slight changes in serum inorganic phosphorus concentration, may be maintained for a period of time. However, as renal function deteriorates further, homeostatic mechanisms fail, phosphorus balance becomes positive, and progressive hyperphosphatemia usually develops.

The association of hyperphosphatemia and kidney dysfunction has been known for over 80 years [2], $Al(OH)_2$ was used to reduce phosphorus levels and heal uremic bone disease in 1941 [3], and metastatic calcification has been attributed to hyperphosphatemia since the early 1960s [4]. However, the clinical impact and toxicity of hyperphosphatemia was not widely emphasized until the groundbreaking studies carried out in the early 1970s by Bricker et al [5, 6]. Using animal models, they delineated the pathophysiologic cascade triggered by hyperphosphatemia, leading to hypocalcemia, secondary hyperparathyroidism, reduced $1,25vitD_3$, and progressive metabolic bone disease. These studies also triggered efforts by clinicians to aggressively attempt control of phosphorous levels in patients with advancing and end-stage kidney disease. The population at risk also increased markedly as hemodialysis became a widely available treatment. Phosphorus control strategies included dietary phosphorus restriction, the ingestion of drugs that bind phosphorus within the GI tract and thereby reduce its absorption, and phosphorus removal with dialysis.

A four-hour hemodialysis treatment may remove about 1000 mg of phosphorus, but this is generally inadequate to restore normal phosphorus levels and phosphorus balance (with the exception of slow, daily, and/or nocturnal hemodialysis, which removes much greater quantities of phosphorus) [7–9]. Therefore, reestablishment of normal phosphorus levels and balance requires a major reduction in phosphorus absorption.

Key words: phosphorus binders, hyperphosphatemia, secondary hyperparathyroidism, vitamin D.

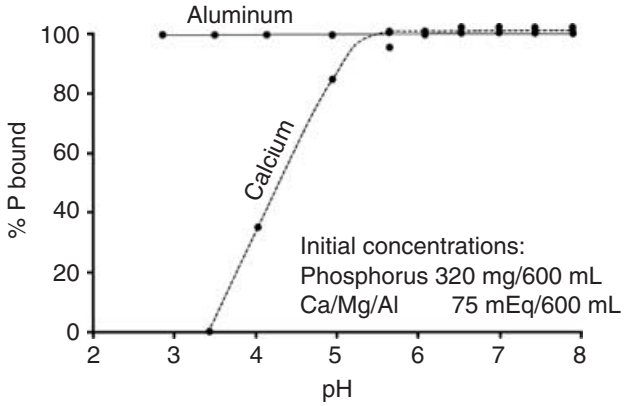

Fig. 1. A theoretical analysis of the effect of pH on the binding of phosphorus by dissolved calcium or aluminum at equilibrium. Aluminum binds virtually all the phosphorus regardless of pH, while calcium binding is seen to be much better above pH 5. Initial concentrations: phosphorus 320 mg/600 mL, calcium or aluminum 75 mEq/600 mL. Adapted from Sheikh et al [12].

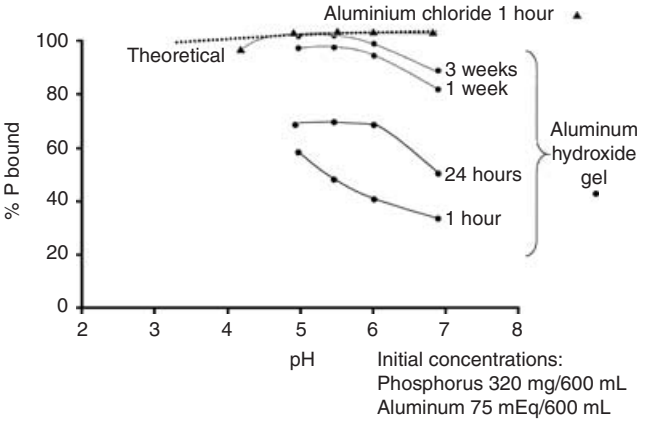

Fig. 2. In vitro phosphorous binding by aluminum hydroxide gel—the effect of pH and time. Aluminum hydroxide gel was added to a beaker containing dissolved phosphate maintained in a shaker bath at 37°C. The pH was adjusted with HCl or NaOH as needed to maintain a constant level. Initial concentrations: phosphorus 320 mg/600 mL, aluminum 75 mEq/600 mL. Adapted from Sheikh et al [12].

This can only be partially accomplished by dietary restriction because most foods contain abundant amounts of phosphorus. Consequently, various phosphorus-binding compounds are usually required to normalize phosphorus levels and balance.

The history of phosphorus binders can be generally divided into three overlapping eras. The first began in the early 1970s, when the importance of phosphorus control was first emphasized, and was characterized by the pervasive use of alkaline aluminum salts. This continued until the early 1980s, when the toxicity of aluminium became widely recognized [10, 11]. The second, the era of calcium salts, started in the early 1980s and has continued through the present time. We are currently in the third phosphorus binder era, represented by introduction of nonmetallic phosphorus binding resins and other novel agents.

Most clinically useful phosphorus binders are hydroxide, carbonate, or acetate salts of metal ions, such as aluminum, calcium, magnesium, and lanthanum. pH affects both the rate of dissolution of the salt and the subsequent binding reaction between the metal ion and phosphate. Generally, a very acidic pH is best to dissolve and ionize the salt. Then, the metal ion must combine with inorganic phosphorus (phosphate), and this reaction may also be pH dependent. The optimal pH for these two reaction steps may be very different. For example, calcium carbonate is most soluble at pH 1 to 3, but calcium to phosphate binding is optimal above pH 5.

ALUMINUM AND CALCIUM SALT PHOSPHORUS BINDERS

Figure 1 shows the theoretical effect of pH on phosphorus binding by aluminum and calcium. These calculations assume that 320 mg of phosphorus, as sodium phosphate, is dissolved in 600 mL of fluid (to approximate the phosphorus content and volume of an average meal), and then mixed with 75 mEq of a very soluble aluminum or calcium salt. Under these conditions, aluminum completely binds the phosphorus, and this reaction is pH independent [12]. However, theoretical calcium-phosphorus binding has major pH dependency, with virtually no binding below pH 3.5, and maximal binding above pH 5. The pH effect on binding between calcium and phosphorus is related to the precipitation constants of various calcium-phosphate compounds and the relative concentrations of H_3PO_4, $H_2PO_4^{-1}$, HPO_4^{-2}, and $PO4^{-3}$ in the solution at any given pH. The theoretical calculations in Figure 1 assume that all of the aluminum or calcium is initially dissolved and ionized.

Aluminum salts

Figure 2 shows the results of comparable in vitro experiments using identical concentrations of phosphorus and aluminum salts [12]. Aluminum chloride, a very soluble and reactive salt, binds phosphorus with near theoretical potency, and binding is relatively independent of pH. However, aluminum chloride is very corrosive, generating HCl when dissolved in water, and therefore cannot be utilized clinically. Alkaline aluminum salts including aluminum hydroxide gel (Amphojel®) or aluminum carbonate (Basaljel®) (both manufactured by Wyeth Laboratories, Collegeville, PA, USA) are well tolerated (at least acutely; see below), and have been used as antacids for many decades. To the extent these salts dissolve and release aluminum ions, they are potent phosphorus binders. However, as shown in Figure 2, phosphorus binding by aluminum hydroxide after 1 to 24 hours was only about 30% to 60% of the theoretical predictions. The difference is due to slow dissolution and ionization of the alkaline aluminum salt. Under these conditions, phosphorus binding is pH dependent with greater

binding in a more acid environment. This occurs because an acid pH is necessary to dissolve the salt and release aluminum ions to bind phosphorus. Similar results (not shown) were seen with aluminum carbonate gel (Basaljel®) and sucralfate (Carafate®; Hoechst Marion Roussel, Kansas City, MO, USA) [12]. Other aluminum salts commercially available in the United States, including ALternaGEL® (Johnson & Johnson, New Brunswick, NJ, USA) and Alu-Caps® (3M, St. Paul, MN, USA), have similar properties.

The effect of aluminum salts on phosphorus absorption was then studied in vivo in normal subjects using a well-characterized GI washout methodology [12]. These studies demonstrated that aluminum carbonate gel (Basaljel®) reduced the absorption of dietary phosphorus from 66% (263 mg of the 345 mg of phosphorus in the meal) to 18% (61 mg of the 345 mg in the meal), confirming the clinical impression that alkaline aluminum salts were very effective GI phosphorus binders. In dialysis patients, aluminum salts reduced dietary phosphorus absorption from 70% to between 35% and 49% [13]. Presumably, the salts dissolve in the stomach and the aluminum ions then bind phosphate released from the food in the stomach and small bowel.

Despite the relative potency of aluminum salts, phosphorus control remained suboptimal for most patients. The large doses required with each meal, the taste, and resulting constipation produced poor medication compliance (even though these drugs were relatively inexpensive). Dietary indiscretion, use of vitamin D preparations that increase GI phosphorous absorption, and endogenous release of phosphorous from bone caused by secondary hyperparathyroidism also contributed to persisting hyperphosphatemia. Nonetheless, aluminum salts were, and probably still are, the most potent phosphorus binders available for clinical use. Unfortunately, the suspicion that aluminum salts might be toxic, first seriously raised in the early 1970s [14, 15], was proven correct [10, 11]. A tiny fraction of the ingested aluminum load is absorbed. With normal kidney function most of the absorbed aluminum is excreted. However, when dialysis patients ingest large quantities of these salts, aluminum accumulates in and damages the skeleton, central nervous system, peripheral nerves, parathyroid tissue, and hematopoietic cells. Progressive and often fatal, skeletal and neurologic dysfunction were the most devastating manifestations of this poisoning. The disease was particularly severe in centers using dialysate contaminated with high levels of aluminum from municipal water supplies. The relative importance of aluminum loading from the dialysate and from ingested medications varied from center to center and among different populations of patients with kidney disease [10, 11]. However, even patients not on dialysis can accumulate toxic levels of aluminum when high doses are ingested, especially if citrate salts, which increase aluminum absorption, are also ingested [16].

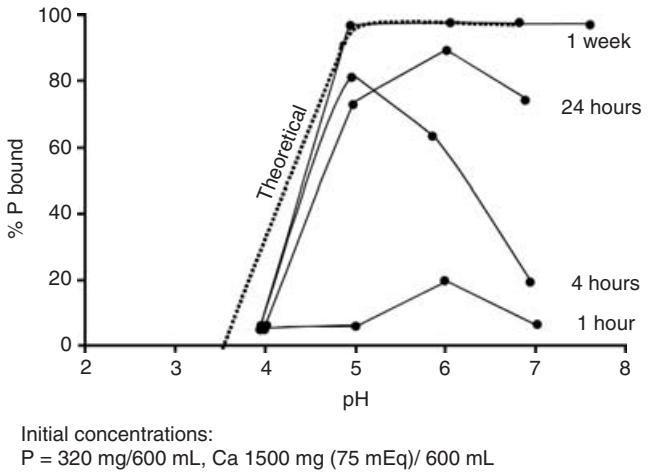

Fig. 3. In vitro phosphorus binding by calcium carbonate—the effect of pH and time. Calcium carbonate was added to a beaker containing dissolved phosphate maintained in a shaker bath at 37°C. The pH was adjusted with HCl or NaOH as needed to maintain a constant level. Initial concentrations: phosphorus 320 mg/600 mL, calcium 75 mEq/600 mL. Adapted from Sheikh et al [12].

Calcium salts

By the early 1980s, nephrologists were aggressively seeking alternative, non-aluminum, phosphorus binders. This ushered in the next phosphorus-binding era, dominated by the calcium salts. It had been known for decades that calcium salts bind dietary phosphorus, albeit less effectively than aluminum [17]. There are at least two reasons that calcium salts are less effective phosphorus binders than aluminum salts. First, unlike ionized aluminum, ionized calcium binding to phosphorus is very pH dependent and decreases sharply below pH 5 (Fig. 1). Simultaneously, calcium carbonate, the most widely used calcium salt, dissolves best in a very acid milieu. Thus, a major problem with calcium carbonate is the opposite effect of pH on solubility and on the calcium-phosphate reaction. Acidity is best for solubility, but binding to phosphorus is best at higher pH. After one hour, in vitro phosphorus binding by calcium carbonate is minimal as a result of the salt's insolubility (Fig. 3). After four hours, in vitro binding has improved, but only around pH 5; binding falls sharply above pH 5 (due to less dissolution of the salt) and below pH 5 (due to less precipitation of calcium with phosphorus) (Fig. 3). Theoretical maximal binding at any pH is not achieved for several days. Therefore, an acid gastric pH is optimal to dissolve calcium carbonate, but a higher pH is needed for the dissolved calcium to bind phosphorus. Further, this data suggests that hypo- or achlorhydria caused by gastritis, common among patients with kidney failure [18], or the use of H_2 blockers or proton pump inhibitors would compromise calcium carbonate dissolution and reduce its efficacy as a phosphorus binder (this may also be true for aluminum salts). Studies addressing this issue in patients report conflicting conclusions [19, 20].

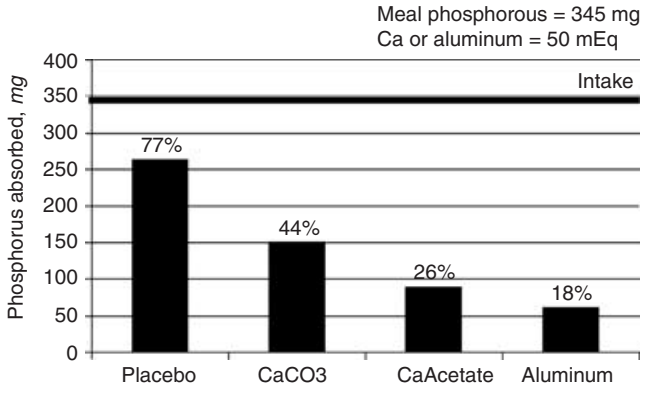

Fig. 4. The effect of ingestion of calcium carbonate, calcium acetate, or aluminum hydroxide gel on the absorption of ingested phosphorus by normal subjects ($N = 10$). Absorption was measured with a one-meal balance technique. The dose of each medication contained 50 mEq of the metal. The numbers above each bar represent the percentage of ingested phosphorus that is absorbed. Adapted from Sheikh et al [12].

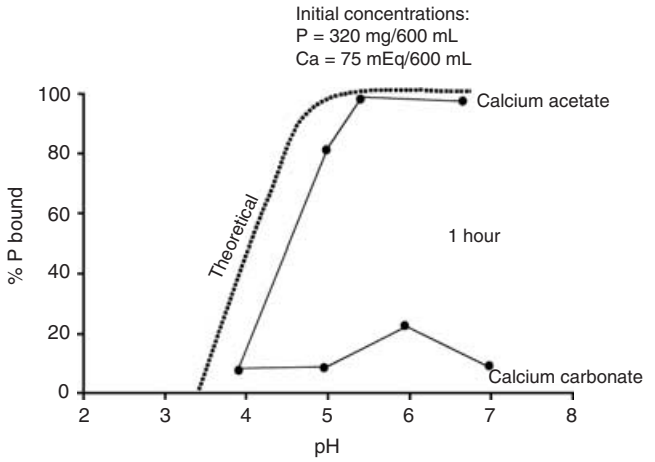

Fig. 5. In vitro phosphorus binding by calcium acetate and calcium carbonate—the effect of pH and time. The calcium salts were added to a beaker containing dissolved phosphate maintained in a shaker bath at 37°C. The pH was adjusted with HCl or NaOH as needed to maintain a constant level. Initial concentrations: phosphorus 320 mg/600 mL, calcium 75 mEq/600 mL, Adapted from Sheikh et al [12].

In vivo studies showed that calcium carbonate bound phosphorus only about half as well as equi-equivalent doses of aluminum salts (Fig. 4) [12]. Despite these disadvantages, calcium carbonate use as a phosphorus binder expanded rapidly because of the increasingly recognized dangers of aluminum toxicity and the lack of better alternatives. However, very high doses of calcium carbonate, averaging >8 to 10 g/day $CaCO_3$ (3.2 to 4.0 g elemental calcium), and more than 17 g/day $CaCO_3$ in some patients, were required to control phosphorus levels [21, 22]. Calcium absorption increases with increasing dietary intake, so these very high calcium doses undoubtedly produced positive calcium balance [23]. Depending on the definition used, hypercalcemia developed in up to one third of dialysis patients treated with high-dose calcium carbonate [21, 22, 24, 25]. It generally resolved quickly when the calcium dose was reduced. To some degree, hypercalcemia could be avoided by reducing dialysate bath calcium concentrations (i.e., to 2.5 mEq/L) [21, 24]. However, the simultaneous use of parenteral or oral vitamin D preparations to suppress parathyroid secretion increased GI calcium absorption and the frequency of hypercalcemia.

The search for safer and more effective phosphorus-binding calcium salts led to the introduction of calcium acetate (PhosLo®; Nabi Biopharmaceuticals, Boca Raton, FL, USA) in 1991 [26]. Calcium acetate is 10,000 times more soluble than calcium carbonate in water [12]. Figure 5 shows that in vitro calcium acetate binding of phosphorus approximates the theoretical calcium-phosphorus binding curve within one hour when calcium carbonate binding of phosphorus remains poor. Short-term balance studies in normal subjects and hemodialysis patients showed that a given dose of elemental calcium administered as calcium acetate bound twice as much phosphorus as the same dose of calcium given as calcium carbonate (Fig. 4) [12, 27]. Multiple long-term large studies of serum phosphorus control in dialysis patients confirmed that half as much elemental calcium is required for phosphorus binding when the acetate salt is used compared with the carbonate salt [26, 28–32].

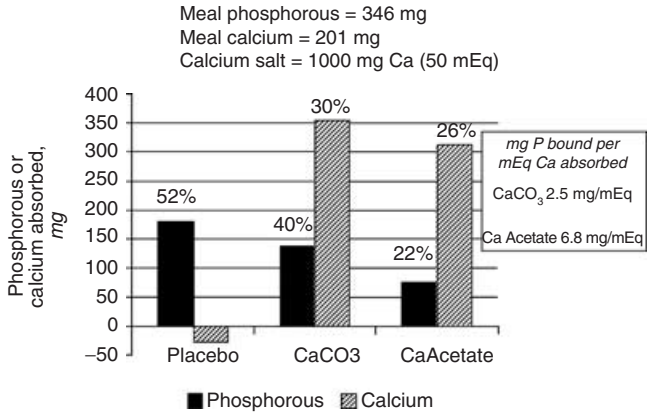

Fig. 6. Effect of ingestion of calcium carbonate or calcium acetate on the absorption of ingested phosphorus and calcium by hemodialysis patients ($N = 6$). Absorption was measured with a one-meal balance technique. The dose of each medication contained 50 mEq of calcium. The numbers above each bar represent the percentage of ingested phosphorus or calcium that is absorbed. Adapted from Mai et al [27].

Short-term studies also indicated that when equal amounts of elemental calcium were given as either calcium acetate or calcium carbonate, the acetate salt bound much more phosphate, and simultaneously significantly less calcium was absorbed (Fig. 6) [12, 27]. The ratio of mg phosphorus-bound/mEq calcium absorbed with calcium acetate was 6.8 compared with 2.5 with calcium carbonate. In other words, more calcium binding to phosphorus means less is available to be absorbed. Therefore, if half

as much calcium could be administered as the acetate salt, it was predicted that less than half as much calcium would be absorbed. If true, this finding would be of critical importance in reducing excess calcium absorption when patients chronically use calcium salts. Unfortunately, the only clinical correlate of calcium absorption that has been studied in long-term comparative human trials is the average serum calcium concentration and the frequency of hypercalcemia. Although some reported a lower frequency of hypercalcemia with the calcium acetate [30, 31], others found no difference [28, 29, 32]. However, calcium concentration and the frequency of hypercalcemia are very indirect indices of calcium absorption or calcium balance. The release of calcium from the skeleton, skeletal buffering of exogenous calcium, bone turnover rate, PTH status, and vitamin D levels are just several factors which affect blood calcium concentration independently of net calcium balance. Some suggest that bone turnover rate may have a greater effect on the development of hypercalcemia in dialysis patients than the oral calcium dose [33].

Other calcium salts including citrate (Citracal®; Mission Pharmacal, Boerne, TX, USA), lactate, gluconate, and essential ketoacid analogues have been studied as potential phosphorus binders [34–38]. None of these have proven to have a significant advantage over calcium carbonate or acetate. Calcium citrate (Citracal®) is a particularly poor phosphorus binder because the citrate anion competes with phosphorus for binding to calcium [12] (this property of citrate is essential to maintain calcium solubility in urine and reduce the risk of calcium oxalate stones). Furthermore, as mentioned above, soluble citrate salts markedly increase GI absorption of trace elements, including aluminum, and thereby greatly elevate the risk of aluminum toxicity if any aluminum salts are also ingested [11, 39].

It is clear that calcium-based phosphorus binders should be ingested together with, or in close temporal proximity to each meal [40]. This strategy maximizes binding of the calcium to dietary phosphorus, and simultaneously minimizes calcium absorption (Fig. 7) [40, 41]. In addition, patients should attempt to tailor each fractional dose of phosphorus binder in proportion to the estimated phosphorus load of each meal [22]. Although these principles have only been well documented for calcium salts, extrapolation to other phosphorus binders is probably appropriate.

The use of any calcium salt in high doses to control serum phosphorus in dialysis patients undoubtedly results in positive calcium balance (i.e., the absorbed calcium load exceeds urine + dialysis calcium losses), and this issue has recently become a point of major concern and debate.

Cardiovascular mortality accounts for about 50% of deaths occurring among dialysis patients [42]. Epidemiologic studies show strong independent correlations between risk of death and either hyperphosphatemia or a high calcium-phosphorus product [43, 44]. Recent studies have also noted that dialysis patients, including very young patients, have a high rate of peripheral and coronary vascular calcification and cardiac valvular calcification [45–50]. While it seems clear that these calcifications are associated with high risk for cardiovascular disease and death, it remains unknown if these vascular calcifications are the cause of disease or merely markers of disease. Further, it is not known if increased GI calcium absorption is the cause of the calcifications or if it directly increases cardiovascular risk. High-dose calcium salt ingestion and high serum calcium concentrations have also been linked to excessive parathyroid suppression and an increasing frequency of adynamic bone disease [51, 52]. All of this has fueled significant concerns about the positive calcium balance that must develop when large doses of calcium salts are ingested, and the effort to minimize calcium absorption and seek non-aluminum, non-calcium phosphorus binder alternatives.

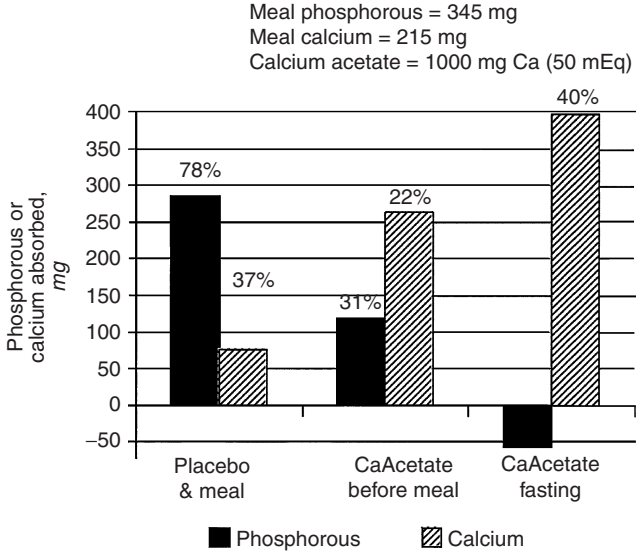

Fig. 7. The effect of time of ingestion of calcium acetate, relative to a meal, on the absorption of phosphorus and calcium in normal subjects ($N = 6$). Absorption was measured with a one-meal balance technique. The dose of calcium acetate contained 50 mEq of calcium. The numbers above each bar represent the percentage of ingested phosphorus or calcium that is absorbed. Adapted from Schiller et al [40].

NON-ALUMINUM, NON-CALCIUM PHOSPHATE BINDERS

Magnesium salts

Both magnesium hydroxide and magnesium carbonate have been studied, and although neither is particularly effective, the carbonate salt is the better phosphorus-binding agent [53–55]. Magnesium salts have two major side effects. First, large amounts of magnesium can be

absorbed and will produce hypermagnesemia. For patients on dialysis, this problem can be ameliorated by reducing or eliminating the dialysate magnesium. Frequent monitoring of blood magnesium levels is required. Equally troubling and difficult to treat or prevent is the diarrhea produced by virtually all magnesium salts when large doses are ingested.

Lanthanum salts

Salts of the rare earth metals lanthanum and zirconium are potentially excellent phosphorus binders, but long-term safety remains of great concern. The chloride salts are toxic but the carbonate salts are better tolerated [56, 57]. Nonetheless, it is likely that small amounts of these metals will be absorbed, and may, when ingested chronically, accumulate and generate toxicity. Several different lanthanum carbonate formulations are being investigated, and Fosrenol™ (Shire Pharmaceuticals, Rockville, MD, USA) is in the final stages of FDA approval. Studies thus far have shown this to be an effective and well tolerated medication. Long-term efficacy and safety studies and cost will be of critical importance in determining the niche this drug will fill among the phosphorus binders.

Iron salts

Numerous ionic and non-ionic iron salts and iron-carbohydrate complexes that have phosphorus-binding properties have been studied in animal models and in small-scale human trials. Although several have clinical potential, none have yet been studied in large numbers of patients, none are approved phosphorus binders, and they are not generally used for this purpose [58–61].

Sevelamer hydrochloride

We have now entered the third phosphorus binder era: binders entirely free of any potentially toxic metals. The first such agent to be marketed is sevelamer hydrochloride (RenaGel®; Genzyme, Cambridge, MA, USA). This cross-linked poly (allylamine HCl) exchange resin binds phosphate and releases chloride. Phosphorus binding is most effective in the pH range between 5 and 7 [62, 63]. As noted, its major advantage is the absence of absorbable metal cations. The drug also has an unanticipated beneficial side effect of binding bile salts, and thereby reducing LDL cholesterol levels [64–66]. Renagel® also has several drawbacks. It is very expensive (>$1.00/tablet, or about $2,500/year when a relatively low dose of 6 tablets are used/day), large quantities are generally required to achieve control (5 to 7 g or 6 to 18 tablets/day, depending on the tablet size), high doses generate GI complaints, although probably not more frequently than from high-dose calcium salts [67], and although no metal is released, some of the chloride released when the resin binds phosphate (or HCO_3) is absorbed together with a proton, and this creates or worsens metabolic acidosis [67, 68]. Several trials comparing RenaGel® with calcium acetate suggest the dose of each drug required for phosphorus control translated to similar medication weight, but phosphorus levels were generally lower with the calcium salt [67–70]. A randomized, double-blind comparison between calcium acetate and Renagel® (the dose of each drug was titrated by the "blinded" physician to attempt adequate phosphorus control) found the calcium salt controlled phosphorus more effectively, and was more likely to produce acceptable phosphorus levels [67]. As expected, the calcium levels were significantly higher with calcium acetate, but because of a greater degree of phosphorus reduction, calcium acetate therapy reduced the calcium-phosphorus product below the level achieved with than RenaGel® (Fig. 8) [67]. Another study comparing Renagel® with calcium salts (both carbonate and acetate) reported that coronary and aortic calcification, measured with electron beam tomography, progressed more rapidly in the calcium treated group [71]. However, due to a number of methodologic concerns, including nonblinding of the study drug, the divergent effects of calcium salts and Renagel® on LDL, the variety of calcium salts used, dialysate calcium concentrations controlled, and a large number of patient dropouts, the interpretation of these results are controversial and await confirmation by better controlled and longer duration studies. It is likely that other more effective, well-tolerated, nontoxic, and hopefully, less expensive phosphorus binders will be introduced over the next few years.

Inhibition of transmucosal phosphorous transport

Another approach, not yet proven to be clinically effective or practical, is inhibition of the small intestinal Na-phosphate transporter. Niceritrol, a nicotinic acid prodrug marketed as a lipid-lowering drug, will reduce the activity of this transporter in rodents and has shown some efficacy in a small preliminary human trial [72, 73].

Finally, until we have much more effective and inexpensive methods to reduce phosphorus absorption, the importance of dietary phosphorus restriction should not be neglected. At this time, a major reduction in phosphorus intake adversely affects dietary palatability, and also may require significant protein restriction. However, avoidance of foods which are very rich in phosphorus, such as dairy products, some carbonated drinks, processed meats, nuts, and some baking powders remains important for most patients with chronic kidney disease.

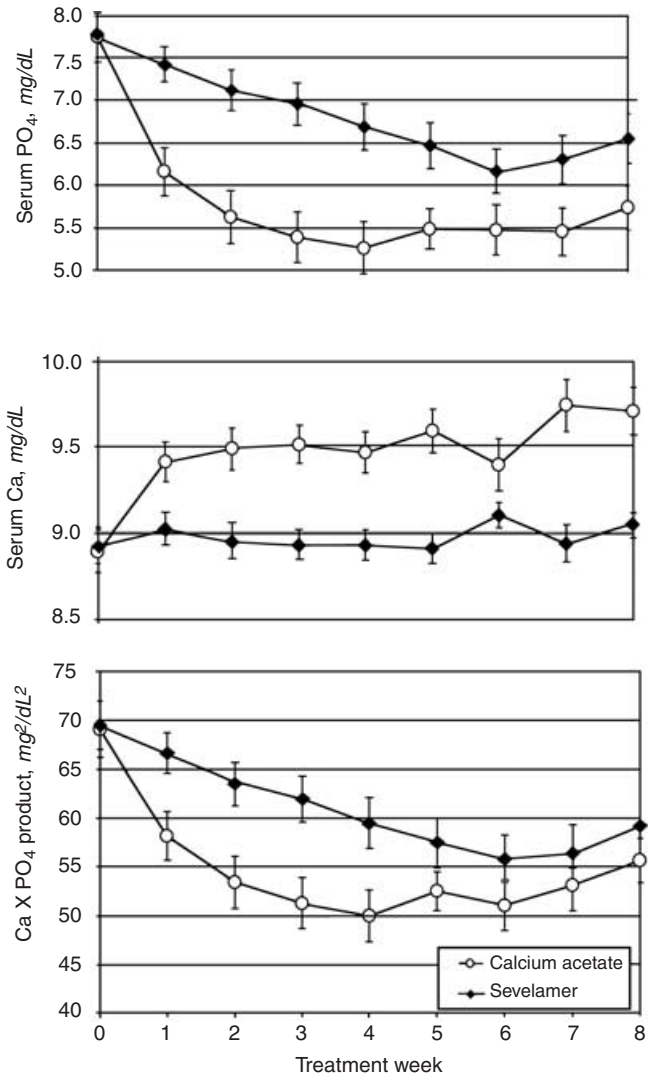

Fig. 8. Mean serum phosphorus and calcium levels and calcium × phosphorus product during treatment with calcium acetate or sevelamer hydrochloride at baseline and after weeks 1 through 8 of therapy. Each data point represents the mean ± standard error. Adapted from Qunibi et al, *Kidney Int*, 2004.

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