

UPDATE ON CALCIUM-FREE PHOSPHATE BINDERS

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Running title: New phosphate binders

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Abbreviations

Al(OH) ₃	Aluminum hydroxide
Ca x P	Calcium x phosphate product
CaCO ₃	Calcium carbonate
Ca-KG	Calcium α -ketoglutarate
CKD	Chronic kidney disease
CNS	Central nervous system
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HD	hemodialysis
HDL-C	High density lipoprotein cholesterol
K/DOQI	Kidney/dialysis outcome quality initiative
La ₂ (CO ₃) ₃	Lanthanum carbonate
LDL-C	Low density lipoprotein cholesterol
Pi	Phosphorus, Phosphate
PTH	Parathyroid hormone
Sevelamer	Sevelamer HCl
TC	Total cholesterol
TG	Triglycerides

Abstract

Phosphate retention and hyperphosphatemia are common complications of end stage renal disease. Disorders of calcium and phosphate metabolism contribute to the increased cardiovascular mortality in this patient population. Phosphate binders are commonly prescribed to control phosphate retention. Hypercalcemia and over-suppression of parathyroid hormone production are common adverse reactions associated with the use of calcium-containing phosphate binders. Although calcium acetate appears to have less deleterious effects on these parameters, the current emphasis has been on the development of calcium and aluminum-free phosphate binders. Sevelamer hydrochloride, an ion exchange resin, was the first such phosphate binder approved for use in patients with end stage renal disease. It can reduce serum phosphorus levels and parathyroid hormone production without inducing hypercalcemia. It also has the added benefit of reducing total and low-density lipoprotein cholesterol levels. Recent studies have shown that sevelamer treatment is associated with stabilization of coronary artery calcifications, while calcium-containing phosphate binders may lead to progression of coronary artery calcification. Disadvantages of sevelamer are its high cost, need for relatively high doses, and the possible induction of metabolic acidosis. Lanthanum carbonate was recently approved for use as a phosphate binder. It is as effective as aluminum hydroxide without neurological or bone-related complications. Like sevelamer, it results in much lower incidence of hypercalcemia. It is generally well tolerated with adverse reactions similar to placebo. Colestimide, another anion exchange resin, originally developed to treat hyperlipidemia, has been found to be an effective phosphate binder. It is not currently approved for use as a phosphate binder.

Mechanism of phosphate retention in CRF

End stage renal disease (ESRD) affects over 431,000 people in the United States ^[1] and ~1.1 million people worldwide. Its incidence has been increasing ~ 5% each year ^[1].

Disorders of calcium and phosphate (Pi) metabolism are a ubiquitous, but difficult to manage, problem in ESRD. Phosphate retention and hyperphosphatemia result from the inability of the diseased kidneys to increase Pi excretion to match the intake.

Hyperphosphatemia is associated with a number of complications including secondary hyperparathyroidism and renal osteodystrophy ^[2, 3], increased mortality ^[4, 5], and accelerated progression of renal failure ^[6, 7].

Phosphorus constitutes a major component of Western diets. The average dietary phosphorus intake is 1000-1200 mg/day, of which about 60% is absorbed. To maintain Pi homeostasis, 600-700 mg of Pi must be excreted in 24 hours. As the glomerular filtration rate (GFR) decreases to levels below 20 ml/min, it becomes difficult for the urinary Pi excretion to match the dietary Pi intake. Assuming that 600 mg of Pi is absorbed daily, to maintain Pi balance at a GFR of 30 ml/min, the serum Pi concentration would have to increase to more than 7 mg/dL (2.26 mmol/L), whereas it would remain below 4 mg/dL (1.3 mmol/L) when the GFR is 50 ml/min (Fig. 1) ^[8]. As the GFR declines further, dietary Pi restriction alone will not be sufficient to maintain Pi balance, even after starting hemodialysis. Assuming a Pi intake of 850 mg/day (30% reduction), weekly hemodialysis Pi removal of 2700 mg (900 mg per 4-h session), and daily urinary Pi excretion of 200 mg (see Fig 1 for GFR \leq 10 ml/min), the weekly Pi balance will be +550 mg. Accordingly, in both chronic kidney disease (CKD) patients and in patients on

dialysis, dietary Pi restriction and the use of Pi binders is necessary to reduce the filtered load of Pi and return serum Pi concentrations toward normal.

Background on phosphate binders

Aluminum-containing phosphate binders are no longer used in ESRD patients. Increased aluminum absorption in ESRD patients has been shown to result in neurological complications and in osteomalacia^[8,9]. Calcium salts are currently the most commonly used Pi binders. The use of calcium-based phosphate binders, particularly calcium carbonate (CaCO_3), has been associated with recurrent episodes of hypercalcemia, oversuppression of parathyroid hormone production, and adynamic bone disease^[10]. Together with high serum Pi levels, hypercalcemia can result in elevated Ca x Pi product. Evidence exists for an association between elevated serum Pi concentration or Ca x Pi product and increased mortality in hemodialysis patients^[5, 11]. Recent efforts, therefore, have focused on the development of Pi binders devoid of calcium and aluminum. The first calcium- and aluminum-free Pi binder approved in dialysis patients was sevelamer hydrochloride (RenaGel[®], Genzyme Corporation, Cambridge, MA). Recently, lanthanum carbonate (Fosrenol, Shire Pharmaceuticals, Hampshire, UK) was also approved for use as a phosphate binder in dialysis patients. Several other compounds are in various stages of development (Table 1). The majority of phosphate binders currently in development are based on metal ions. The long term consequences of accumulation of metals on patient safety remains unknown^[8, 9, 12].

When treating hyperphosphatemia, the Ca x Pi product should be maintained below 55 mg²/dL² (4.4 mmol²/L²)^[3]. Serum phosphorus must be kept between 3.5 - 5.5 mg/dL (1.77 mmol/L). The recommended range for albumin-corrected serum calcium is 8.4 to 9.5 mg/dL (2.1 to 2.38 mmol/L). Intact PTH levels should be maintained between 150 – 300 pg/mL (15.9 – 31.8 pmol/L)^[3, 13]. For a variety of reasons, which include the necessity to change long-established dietary habits, poor adherence with phosphate binders, and short dialysis times, these targets have been difficult to achieve. In a single center study including 152 hemodialysis patients, phosphorus target range was achieved 36% of the time and PTH levels were within targets in only 20% of measurements^[14]. These recommendations are based on epidemiological studies; therefore, their validity will require long-term outcome research.

Calcium-containing phosphate binders

Currently, the most widely used Pi binders are calcium salts, including CaCO₃ and calcium acetate^[15, 16]. Hypercalcemia is often associated with the use of calcium-containing Pi binders in conjunction with oral or intravenous calcitriol and a high dialysate calcium bath. Over-suppression of PTH production secondary to chronic hypercalcemia is a major factor in adynamic bone disease [10, 17]. Among various calcium salts, CaCO₃ has the highest level of elemental calcium (40%) and its use as a phosphate binder has been associated with the highest incidence of hypercalcemia. Calcium acetate (PhosLo[®], Nabi Pharmaceuticals, Boca Raton, FL) has a lower elemental calcium (25%) and higher Pi binding capacity than CaCO₃. As a result, the incidence of hypercalcemia is lower with calcium acetate than with CaCO₃^[18, 19].

The chronic use of calcium-containing Pi binders has been associated with coronary artery calcifications [11, 13]. In hemodialysis patients, a direct correlation has been found between oral calcium dose prescribed and the number of vascular calcification sites [20]. Furthermore, the presence and the extent of vascular calcifications is a predictor of mortality in this patient population [21].

Calcium α -ketoglutarate

Calcium α -ketoglutarate is an analogue of glutamic acid which was reported to bind phosphate efficiently [22]. Because of putative anabolic and nitrogen sparing effects, calcium α -ketoglutarate has been used to improve nutritional status of malnourished patients [23]. In a randomized cross-over study in 28 hemodialysis patients [24], the incidence of hypercalcemia (serum Ca >2.8 mmol/L) (>11.2 mg/dL) was higher with calcium acetate than with calcium α -ketoglutarate ($p = 0.03$) (Table III). Due to higher Pi binding capacity, lower doses of calcium α -ketoglutarate than calcium acetate may be required to control hyperphosphatemia. The likelihood of hypercalcemia in descending order is: Ca citrate > CaCO₃ > Ca acetate > Ca α -ketoglutarate. Calcium α -ketoglutarate is not currently approved in the United States for use as a phosphate binder [25].

Sevelamer hydrochloride (RenaGel[®])

Pre-clinical studies

Sevelamer hydrochloride (RenaGel[®], Genzyme Corp., Cambridge, MA) was the first aluminum-free and calcium-free Pi binder approved for control of hyperphosphatemia in

patients with end-stage renal disease ^[26]. Sevelamer is a cationic polymer [poly(allylamine hydrochloride)] that binds phosphate by ion exchange and hydrogen bonding. Sevelamer binds approximately 2.5 - 2.7 mmol Pi per gram (in the presence of 5 mM Pi, pH 7.0) with maximum binding reached between pH 6 and 8 ^[27] (Table I). It is not absorbed by the gastrointestinal tract and the phosphate-resin complex is excreted in the feces ^[28]. A novel feature of sevelamer is its ability to bind and sequester bile acids, a property that may account for its ability to lower serum cholesterol levels ^[29] (see below). When exposed to gastric and intestinal fluids, the gel undergoes hydration and swells to ~6 - 8 times its dry weight ^[30]. Adequate fluid intake is, therefore, necessary when taking sevelamer. Preliminary *in vitro* studies suggest that, prior exposure of sevelamer HCl to an acidic pH, results in increased protonation and increased solubility ^[31]. This may prime the resin to bind more phosphate per unit weight. Reduced gastric acidity in patients treated with proton pump inhibitors could theoretically reduce the Pi binding efficiency of sevelamer. Preliminary *in vitro* studies show that sevelamer is able to adsorb the protein-bound uremic toxin, indoxyl sulfate ^[32]. Additional studies are needed to determine if this could translate into clinically significant benefits.

Initial preclinical studies in rats, receiving sevelamer HCl mixed with their diet, showed dose dependent reduction in urinary Pi excretion, indicating binding of dietary phosphorus by the gel ^[30]. In a nephrotoxic model of chronic renal insufficiency, 3% sevelamer for 84 days, reduced serum Pi concentration, arrested parathyroid hyperplasia and prevented the development of secondary hyperparathyroidism ^[33].

Clinical studies of sevelamer

In a placebo-controlled dose finding study in 24 healthy volunteers, sevelamer administered for 18 days led to inhibition of dietary Pi absorption ^[34]. At the two highest doses (2.5 and 5.0 g three times a day), sevelamer resulted in a significant increase in fecal Pi excretion and reduction of urinary Pi excretion compared to placebo. There was also a significant reduction in serum cholesterol concentrations in the sevelamer-treated group.

Chertow *et al.* ^[35] performed a placebo-controlled randomized clinical trial in 36 hemodialysis patients receiving sevelamer for 2 weeks. They observed a significant reduction of serum Pi concentrations compared to placebo ^[35]. Serum Pi declined 1.2 mg/dL (0.38 mmol/L) in the sevelamer group and increased 0.2 mg/dL (0.06 mmol/L) in the placebo group. This short study demonstrated the ability of sevelamer to lower serum Pi concentrations.

Slatopolsky *et al.* ^[36] performed a multicenter open label dose finding study of 172 hemodialysis patients. After a 2-week washout period, the patients received 3 different doses of sevelamer for 8 weeks. The dose was titrated every 2 weeks. After 8 weeks, the mean serum Pi concentration declined from 9.1 ± 1.9 mg/dL (2.94 ± 0.77 mmol/L) to 6.6 ± 1.9 mg/dL (2.13 ± 0.61 mmol/L) ($p < 0.0001$). At the end of 8-week treatment, median serum PTH level declined from 316 pg/ml to 224 pg/mL ($p < 0.0001$) ^[36]. The average sevelamer dose was 5.4 g/day. This short-term study established the effective dose of

sevelamer for control of hyperphosphatemia in patients receiving hemodialysis treatments.

In an open label dose titration study, sevelamer was administered for 8 weeks to 48 hemodialysis patients. The dose was increased every 2 weeks to achieve the desired serum Pi concentration ^[37]. Serum Pi reached the nadir of 6.5 mg/dL (2.1 mmol/L) after 7 weeks of treatment. Serum PTH levels declined from a mean of 395 to 283 pg/ml (41.9 to 30 mmol/L). There was also a decline in serum TC and LDL-C concentrations ^[37]. In another open label study involving 15 hemodialysis patients, sevelamer was again administered for 8 weeks with the dose titrated at 2-week intervals to maintain serum Pi concentrations below 5.5 mg/dL (1.77 mmol/L) ^[38]. This study confirmed that sevelamer can lower serum Pi concentrations and result in reduced serum PTH levels. The beneficial effects of sevelamer on the lipid profile were also confirmed.

Chertow *et al.* treated 192 hemodialysis patients with sevelamer ^[39]. After 2 weeks washout, the patients were treated with sevelamer for 44 weeks ^[39]. The dose of sevelamer was titrated monthly. The analysis was based on three pre-specified sevelamer doses: low (<5.0 g), medium (5.0 - 6.75 g) and high (>6.75 g). The mean sevelamer dose was 6.3 g/day. Serum Pi declined from 2.8 ± 0.71 mmol/L (8.7 ± 2.2 mg/dL) at baseline to 2.06 ± 0.6 mmol/L (6.4 ± 1.8 mg/dL) at the end of treatment ($p < 0.0001$). The mean change in serum Pi concentration from baseline was -0.71 ± 0.77 mmol/L (-2.2 ± 2.4 mg/dL) and the mean change in Ca x Pi product was -18.1 ± 22.0 mg²/dL² (-1.46 ± 1.78

mmol^2/L^2) ($p < 0.0001$)^[39]. The reduction in Ca x Pi was most pronounced in the high dose group.

In a single center open label study, sevelamer (3.1 ± 0.9 g/day) was administered to 19 hemodialysis patients for 6 weeks^[40]. At the end of the study, serum calcium declined from 9.2 ± 0.5 mg/dL to 8.7 ± 0.6 mg/dL (2.30 ± 0.12 to 2.17 ± 0.15 mmol/L) ($p < 0.01$). There was also a significant reduction in Ca x Pi product (from 64.1 ± 14.1 to 46.9 ± 7.4 mg^2/dL^2) (5.17 ± 1.14 to 3.78 ± 0.6 mmol^2/L^2)^[40].

Mahdavi *et al.*^[41] performed a 6-month open label trial of sevelamer in 14 children receiving peritoneal dialysis and 3 children receiving hemodialysis treatment who were previously treated with calcium-containing Pi binders. The mean age was 11.8 ± 3.7 years. The number of children on CaCO_3 and calcium acetate was not specified. After a 2-week washout, the patients received sevelamer (4.5 ± 5 g/day), which was titrated to achieve Pi control and maintained for 6 months. Twelve patients completed the study. Serum Pi decreased from a baseline of 7.5 ± 2.2 mg/dL to 6.3 ± 1.5 mg/dL (2.42 ± 0.71 to 2.03 ± 0.48 mmol/L) at the end of the study. Despite a relatively high sevelamer dose of 6.7 ± 2.4 g/day, serum Pi levels remained above the recommended target of < 5.5 mg/dL (< 1.77 mmol/L). Serum calcium levels were comparable to baseline and Ca x Pi product remained below the baseline.

Among the studies listed above, one was placebo-controlled while the others were uncontrolled dose-finding studies. Subsequent studies have compared the efficacy of

sevelamer treatment to standard of care, which at the time of these studies, included CaCO_3 and calcium acetate.

In an open label cross-over study of 84 hemodialysis patients, sevelamer was compared with calcium acetate for its ability to lower serum Pi concentrations ^[42]. After a 2 week washout, the patients received either sevelamer or calcium acetate for 8 weeks. The dose was titrated every 2 weeks to achieve a serum Pi <5.5 mg/dL (<1.77 mmol/L). The patients then entered another 2 week washout and then assigned to the alternate treatment for 8 weeks. The mean change in serum Pi concentration from baseline was comparable between the two treatments [(-2.0 ± 2.3 mg/dL versus -2.1 ± 1.9 mg/dL) (0.64 ± 0.74 vs 0.68 ± 0.61 mmol/L) for sevelamer and calcium acetate, respectively]. The mean sevelamer dose at study end was 3.1 ± 0.6 g/day. Hypercalcemic episodes, defined as at least one serum calcium >11.0 mg/dL (>2.75 mmol/L), were much less frequent with sevelamer than with calcium acetate (5% for sevelamer versus 22% for calcium acetate). This study also showed significantly lower serum TC and LDL-C levels with sevelamer treatment but no change with calcium-acetate treatment (p<0.0001 for both).

When used in patients also receiving active vitamin D analogues, sevelamer can suppress parathyroid hormone secretion without affecting serum calcium concentrations. In a randomized controlled parallel group study, Salusky *et al.* ^[43] compared the effect of treatment with CaCO_3 or sevelamer in 29 children receiving peritoneal dialysis treatment. The patients also received oral calcitriol or intravenous doxercalciferol for 8 months, followed by bone biopsy. PTH levels declined with both drugs, although sevelamer-

treated patients had higher PTH levels compared to CaCO₃-treated patients (562 ± 164 versus 369 ± 92 pg/mL). Bone formation was normalized in ~ 75% of patients in both groups. It must be noted that these PTH levels are above the generally recommended levels in CKD patients [3, 44].

Chertow *et al.* [45] conducted a randomized clinical trial in 200 hemodialysis patients, comparing sevelamer with a calcium-based phosphate binder administered for 52 weeks. Calcium acetate was used at US centers and CaCO₃ at European centers. The dose of Pi binder was titrated every 3 weeks to achieve serum Pi and calcium concentrations in the target range. Calcification scores for coronary arteries and for the aorta were determined by electron beam tomography (EBT). Serum Pi concentrations were equally controlled with the two treatments but serum calcium concentrations were higher in the calcium-treated group (9.5 ± 0.6 versus 9.7 ± 0.7 mg/dL (2.37 ± 0.15 vs 2.42 ± 0.17 mmol/L), respectively; $p=0.002$). The incidence of hypercalcemia was 17% in sevelamer-treated patients compared with 43% in calcium binder-treated patients [45]. The median absolute calcium scores in the coronary arteries and the aorta were significantly higher in calcium binder-treated patients, but remained unchanged in sevelamer-treated patients ($p = 0.03$ and $p = 0.01$, for coronary artery and aorta, respectively) [45].

Block *et al.* [46] studied 129 patients new to hemodialysis, randomized to receive either sevelamer or a calcium-containing Pi binder. Management of mineral metabolism and dyslipidemia was according to center practice. Coronary artery calcification scores were assessed by EBT at baseline and again at 6, 12, and 18 months. At baseline, 37% of

sevelamer-treated and 31% of calcium-treated patients had no detectable coronary artery calcification. Patients with no evidence of coronary artery calcification (zero score) did not show progression of calcification. Those with calcium scores >30 at baseline showed evidence of progression with both treatments. However, those treated with calcium-containing Pi binders had more rapid and more pronounced increases in calcification scores compared to patients treated with sevelamer.

Calcium acetate contains less elemental calcium than CaCO_3 (25% versus 40%), thus putting in question the conclusions based on pooled data from these two calcium-containing Pi binders. To address this issue, a separate analysis including only the US patients treated with calcium acetate has been reported ^[47]. In this analysis, there were no differences between serum calcium concentrations ($p = 0.39$), Ca x Pi product ($p = 0.59$), or serum PTH levels ($p = 0.6$) between calcium acetate- and sevelamer-treated patients. However, there were more hypercalcemic episodes (serum Ca ≥ 10.5 mg/dL) (2.63 mmol/L) with calcium acetate compared to sevelamer (36% vs 13%, $p = 0.015$). Higher coronary artery and aortic calcification scores were found in the calcium acetate-treated subjects, while there were no changes in calcification scores in sevelamer-treated subjects ($p < 0.002$ and < 0.0001 , respectively) ^[47]. In this study, there were also improvements in the lipid profile of patients treated with sevelamer with no change in patients receiving calcium acetate.

Whether calcium acetate is more likely to cause hypercalcemia than sevelamer has been challenged. Qunibi *et al.* ^[48] conducted a double-blind randomized controlled study to

determine the Pi binding efficacy of calcium acetate compared to sevelamer. Ninety-eight stable hemodialysis patients were randomized to receive either calcium acetate or sevelamer HCl. The study included up to 3-weeks washout and 8-weeks treatment. The starting dose of study medications was determined by the serum Pi levels at the end of the washout period. Dose adjustments were performed to achieve a serum Pi concentration of ≤ 5.5 mg/dL (≤ 1.77 mmol/L). The dose of vitamin D analogues and the dialysate calcium concentration (2.5 mEq/L = 1.25 mmol/L) remained unchanged throughout the study. After 8 weeks of treatment, there were no differences in PTH levels between the two groups. Calcium acetate-treated patients had lower mean serum Pi concentrations and lower mean Ca x Pi product, despite higher mean serum calcium concentrations. This study also better defined the degree of metabolic acidosis reported in patients treated with sevelamer. After 8 weeks of treatment, the mean serum bicarbonate level was 21.0 ± 2.6 mmol/L with calcium acetate and 19.3 ± 2.7 mmol/L with sevelamer ($p < 0.0001$). At the end of the study, the mean dose of calcium acetate was 7.1 ± 5.0 g/day compared to 6.6 ± 3.6 g/day for sevelamer. Since sevelamer was offered as 403 mg capsules, the total pill burden was higher for sevelamer-treated patients compared to calcium acetate treated patients.

Non-phosphate binding properties of sevelamer

An additional therapeutic effect of sevelamer is its ability to bind and sequester bile acids [29] resulting in a favorable lipid profile. The effect of sevelamer on serum lipids was evaluated as a secondary endpoint in studies aimed at demonstrating the Pi binding efficacy of the drug [35, 36, 37, 38, 39, 49].

In a dose-titration study of 12 hemodialysis patients receiving sevelamer for 8 weeks, there was 23% fall in TC and 35.9% fall in LDL-C. HDL-C and fat-soluble vitamins were not affected ^[38]. In a longer term study of 46 weeks duration, sevelamer reduced LDL-C 30% and increased HDL-C 18% from baseline ^[39].

Blair *et al.* ^[50] performed an integrated analysis of 493 patients enrolled in clinical trials of sevelamer for reduction of serum phosphorus, including patients already receiving statins. While there were significant reductions in LDL-C and TC in patients receiving sevelamer alone or sevelamer plus statins, a significant increase in HDL-C was seen only in patients treated with sevelamer alone. Burke *et al.* ^[51] performed a meta-analysis of the therapeutic effects of sevelamer, based on 17 published studies. They found average reductions of 30.58 mg/dL (0.79 mmol/L) in TC, 31.38 mg/dL (0.81 mmol/L) in LDL-C, 22.04 mg/dL (0.57 mmol/L) in TG, and 4.09 mg/dL (0.10 mmol/L) average increase in HDL-C.

Ferramosca *et al.* ^[49] performed an evaluation based on 108 US participants of Treat-to-Goal Study ^[45], an open-label, multicenter, long-term randomized trial comparing sevelamer with calcium-based Pi binders. The control patients from US centers were treated with calcium acetate. Assessments for TC, LDL-C and HDL-C were performed at 12, 24, and 52 weeks of maintenance treatment. In addition to serum lipids, markers of inflammation and other cardiovascular and atherogenic risk factors such as high-sensitivity C-reactive protein (hs-CRP), homocysteine, and β_2 -microglobulin were

measured at baseline and at 52 weeks. The average sevelamer dose was 6.5 ± 2.9 g/day and average calcium acetate dose was 4.3 ± 2.2 g/day. In sevelamer-treated patients, there were significant decreases in hs-CRP and β_2 -microglobulin, TC, LDL-C and apolipoprotein B with a significant increase in HDL-C. No changes in the same parameters were observed in calcium acetate-treated patients ^[49].

Because increased triglycerides and LDL-C, and reduced HDL-C are commonly observed in patients with chronic renal failure ^[52], the lipid-lowering effect of sevelamer may be advantageous in such patients. Sevelamer might therefore have the ability to reduce cardiovascular complications by at least three independent mechanisms: improvement in the lipid profile, reduction of inflammatory markers, and prevention of Pi-induced vascular calcifications ^[45, 53].

Adverse reactions to sevelamer

Sevelamer is generally well tolerated with adverse events similar to placebo or to calcium acetate ^[54]. The adverse events that may be possibly related to the drug are nausea (7%), constipation (2%), diarrhea (4%) and dyspepsia (5%) ^[54]. They compare favorably with other available phosphate binders.

Transient declines in serum bicarbonate levels were reported in a study of 16 stable hemodialysis patients receiving a relatively low dose of sevelamer (2.0 g/day) ^[55].

Sonikian *et al.* ^[56] performed a retrospective analysis of 17 hemodialysis patients receiving sevelamer (mean dose 5.5 ± 3.4 g/day) and 7 patients receiving CaCO_3 and

$\text{Al}(\text{OH})_3$. After 2 years of treatment, they observed significantly lower serum bicarbonate concentrations in patients treated with sevelamer (17.9 ± 2.3 mmol/L) compared to those treated with other phosphate binders (19.0 ± 3.3 mmol/L). The retrospective nature of the study, the small number of control subjects, and the pooling of data for CaCO_3 or $\text{Al}(\text{OH})_3$ make the interpretation of the data somewhat difficult.

In a recently completed randomized controlled double blind study to compare the efficacy of calcium acetate and sevelamer (Calcium Acetate Renagel Evaluation, CARE)^[48], 98 patients were equally assigned to receive either calcium acetate or sevelamer HCl for 8 weeks. At the completion of the study, serum bicarbonate levels increased to 21.0 ± 2.6 mmol/L with calcium acetate but decreased to 19.3 ± 2.7 mmol/L with sevelamer. These values are clearly below the 22 mmol/L recommended by K/DOQI guidelines^[3], raising concern that they may lead to increased bone resorption.

The mechanism of metabolic acidosis in patients receiving sevelamer appears to be a combination of withdrawal of a source of base and an increase in net acid production due to release of HCl. The latter occurs following binding of phosphate or bile acids to the gel^[57]. Metabolic acidosis is more likely to occur at higher sevelamer doses or in pre-dialysis patients, since dialysis can partially correct the acidosis. Providing alkali in the form of sodium bicarbonate will correct the acidosis but might reduce the phosphate binding efficacy of sevelamer, as bicarbonate could compete with phosphate anion for binding to sevelamer^[57]. Another suggested approach to neutralizing the excess acid is to increase the dialysate bicarbonate concentration^[58]. Correction of acidosis will also

lower serum potassium concentrations, which may increase with metabolic acidosis. Long-term studies in large numbers of patients are needed to determine if such approaches can be safely applied.

Patients treated with sevelamer must take a large number of capsules with meals to obtain the desired effect. In a long-term study of sevelamer the average daily dose was 6.3 g, which translates to 16 capsules a day^[39]. A high pill burden has been shown to reduce patient adherence and persistence with chronically administered medications^[59]. The recent introduction of 800-mg tablets may partially solve this problem.

Cost considerations

Sevelamer is more expensive than calcium-containing Pi binders, a problem which prevents its use in countries with limited healthcare resources. To reduce costs, it has been suggested to combine sevelamer with a calcium-containing phosphate binder, each used at a lower dose than would be required if used as monotherapy. McIntyre *et al.*^[60] performed a prospective study of the effect of combination calcium-based Pi binder and sevelamer for 8 weeks in 23 hemodialysis patients with mild hypercalcemia. Fifty percent of calcium dose was replaced with an equivalent dose of sevelamer. After 4 weeks, a further 50% exchange with sevelamer was allowed in patients whose serum Ca concentrations remained >2.6 mmol/L (> 10.8 mg/dL). Serum calcium concentrations fell from a mean of 2.8 ± 0.04 to 2.56 ± 0.03 mmol/L (11.2 ± 0.16 to 10.24 ± 0.12 mg/dL) ($p < 0.0005$). This was associated with a marked reduction in episodes of hypercalcemia (26% versus 100%). There was no significant change in serum Pi

concentration. Serum PTH levels increased from 166 ± 47 to 276 ± 104 pg/mL (17.6 ± 5.0 to 29.3 ± 11 pmol/L) ($p=0.02$). By the end of the study, the median sevelamer dose was ~ 2.8 g/day, about half that required to control hyperphosphatemia when sevelamer is used alone^[42]. This study demonstrated that significant cost savings can be achieved with equal control of serum Pi concentrations and with an acceptable calcium load.

In another study by Sturtevant *et al.*^[61], 25 dialysis patients, already on a number of different Pi binders, were started on sevelamer 403 mg three times a day with the dose titrated during a 3-month period to achieve a serum Pi <1.8 mmol/L (5.6 mg/dL), then maintained on the effective dose for another 3 months. At the end of the study, there were no significant changes in serum PTH or calcium concentrations, but significant reductions in serum Pi concentration and in Ca x Pi product. However, only 38% of those completing the study achieved the recommended serum Pi target of <1.8 mmol/L (5.6 mg/dL). The average sevelamer dose was 2.4 g/day. Despite the lower dose, there were still reductions in total and LDL-C concentrations. Gastrointestinal symptoms were the most common adverse events, occurring in 72% of the subjects.

Lower serum calcium concentrations observed in patients receiving sevelamer compared to those receiving calcium-containing phosphate binders are associated with higher PTH levels in sevelamer-treated patients. To overcome this problem, Chertow *et al.*^[62] performed a study where calcium was supplied without a meal to 71 hemodialysis patients, receiving sevelamer as a phosphate binder. The provision of 900 mg elemental calcium each night resulted in better control of hyperparathyroidism without significant

change in serum calcium concentrations ^[62]. Preliminary evidence suggests that the incidence of adynamic bone disease might be lower with combination therapy compared with calcium-based binders used alone ^[63].

In summary, sevelamer HCl is a calcium- and aluminum-free Pi binder based on a novel chemical structure. It is not absorbed and shows a high binding capacity for Pi. Its efficacy and safety have been demonstrated in several well conducted clinical studies. Sevelamer results in significantly lower incidence of hypercalcemia compared to CaCO₃ or calcium acetate. An additional benefit of sevelamer is its ability to lower serum LDL-C and TC concentrations. The use of sevelamer is associated with a reduction in vascular calcification scores, which may in turn result in lower mortality in ESRD patients. The disadvantages of sevelamer are its high cost and the induction of mild metabolic acidosis.

Lanthanum carbonate (Fosrenol[®])

Pre-clinical studies

The use of rare earth metals, lanthanum and zirconium, as possible phosphate binders, was first advocated by Graff and Burnel ^[64, 65]. Lanthanum chloride hydrate, administered to rats with normal renal function, was found to be effective in reducing intestinal Pi absorption. Plasma Pi concentration decreased from 8.7 ± 0.49 mg/dL (2.8 ± 0.16 mmol/L) in controls to 6.4 ± 0.5 mg/dL (2.0 ± 0.16 mmol/L) in the lanthanum-treated rats ($p < 0.01$) ^[64]. In longer studies (3-weeks), the drug was found to accumulate in several tissues with highest levels in the liver ^[64].

Lanthanum (La) is a naturally occurring rare earth metal with multiple industrial applications. It is used extensively in carbon lighting applications such as studio lighting and projection. It is also used to improve the alkali resistance of glass and in the manufacturing of specialty optical lenses^[66,67]. Lanthanides have been shown to block calcium channels in human and animal cells^[68]. High concentrations of lanthanum chloride have been associated with toxicity in cell culture systems (LC50 = 52 μ M = 12.75 μ g/ml)^[69]. Neurodevelopmental defects have been observed in newborn mice exposed to lanthanum chloride during conception and for 30 days postnatally^[70]. Although lanthanum salts may appear toxic under certain conditions, lanthanum chloride and not lanthanum carbonate $\text{La}_2(\text{CO}_3)_3$ was used in these studies. When used *in vivo*, lanthanum does not cross the blood-brain barrier^[71]. Finally, the concentrations of lanthanum used in the above experiments are >1000-fold higher than those found in human tissues during clinical trials of $\text{La}_2(\text{CO}_3)_3$.

A recent study in two rat models of chronic renal failure showed increased tissue lanthanum accumulation when $\text{La}_2(\text{CO}_3)_3$ (3% per weight) was added to the diet for 28 days^[72]. Whether tissue lanthanum accumulation can result in toxic adverse effects is not clear.

The preliminary results of pharmacological and toxicological studies of $\text{La}_2(\text{CO}_3)_3$ have now been released^[73]. Mice, rats, and dogs dosed orally with up to 2,000 mg/kg/day of $\text{La}_2(\text{CO}_3)_3$ showed no acute or chronic adverse CNS effects. Similarly, no acute CNS effects were observed in acute experiments with intravenous $\text{La}_2(\text{CO}_3)_3$ doses resulting in

plasma concentrations ~18,000 times higher than those observed in dialysis patients ^[71].

These pre-clinical findings have now been supported by extremely low incidence of CNS adverse events in patients treated with $\text{La}_2(\text{CO}_3)_3$ for up to 3 years.

Based on its favorable toxicity profile, lanthanum carbonate ($\text{La}_2(\text{CO}_3)_3$) was selected for development as a phosphate binder. Lanthanum carbonate (Fosrenol[®], Shire Pharmaceuticals, Hampshire, UK) was approved in October 2004 by the US Food and Drug Administration for use as a phosphate binder in patients with end stage renal disease. Fosrenol[®] contains $\text{La}_2(\text{CO}_3)_3$ (2:3) hydrate with molecular formula $\text{La}_2(\text{CO}_3)_3 \cdot x \text{H}_2\text{O}$ (on average $x = 4 - 5$ moles of water) and molecular weight 457.8 daltons (anhydrous mass). Chewable tablets contain $\text{La}_2(\text{CO}_3)_3$ hydrate equivalent to 250 or 500 mg of elemental lanthanum ^[74].

$\text{La}_2(\text{CO}_3)_3$ binds phosphate across the pH range 1 – 7, with optimal binding between pH 3 – 7 (Table 1). The Pi binding capacity of La carbonate is similar to that of aluminum hydroxide. This offers an advantage over CaCO_3 , whose Pi binding efficiency drops precipitously at $\text{pH} < 3.5$, due to competition of H^+ ions with Pi ^[75]. Contrary to aluminum, the gastrointestinal absorption of $\text{La}_2(\text{CO}_3)_3$ is very limited. Oral bioavailability in man is $0.00089 \pm 0.00084\%$, which is considerably less than that for aluminum ^[63, 67, 76], resulting in 10 - 50-fold lower bone concentrations than are observed with aluminum ^[63]. Following oral administration, the majority of the drug (99.4%) is excreted in the feces. In rats, a significant amount of drug can be excreted in bile, and some excretion occurs into the gut lumen ^[76].

Clinical studies of lanthanum carbonate

$\text{La}_2(\text{CO}_3)_3$ was evaluated in a placebo-controlled dose finding study in 145 hemodialysis patients^[77]. The patients received doses ranging from 225 to 2250 mg/day elemental lanthanum for up to 6 weeks. There was a dose-dependent decrease in serum Pi levels which was statistically significant for doses of 1350 and 2250 mg. Blood lanthanum levels at the end of the study were 0.10 ± 0.23 ng/mL (0.72 ± 1.66 nmol/L) for placebo and ranged from 0.23 ± 0.23 to 1.16 ± 1.91 ng/mL (1.66 ± 1.66 to 8.35 ± 13.75 nmol/L) for the lowest to the highest dose of $\text{La}_2(\text{CO}_3)_3$. Most common adverse events were nausea and vomiting which occurred in 39% of $\text{La}_2(\text{CO}_3)_3$ -treated patients and 44% of the placebo group^[77].

In a randomized placebo-controlled parallel group study, Joy *et al.*^[78] used $\text{La}_2(\text{CO}_3)_3$ in 126 hemodialysis patients. Following a washout period of up to 3 weeks, the patients entered a 6-week dose titration phase, followed by a 4-week maintenance phase^[78]. Lanthanum doses ranged from 1500 to 3000 mg a day. Hyperphosphatemia, defined as a serum Pi concentration >5.9 mg/dL (>1.9 mmol/L), was controlled in 59% of patients receiving lanthanum versus 23% of those on placebo. Mean serum Pi decreased from 7.69 mg/dL (2.48 mmol/L) to 5.49 ± 1.48 mg/dL (1.8 ± 0.47 mmol/L). The difference between lanthanum- and placebo-treated patients was statistically significant ($p < 0.0001$). The most common adverse events were nausea and vomiting occurring in 6% of lanthanum-treated patients. Serum lanthanum concentrations increased from baseline (maximum 0.776 ng/ml = 5.57 nmol/L).

Al-Baaj *et al.* ^[79] performed a randomized, double blind controlled trial to determine the efficacy of $\text{La}_2(\text{CO}_3)_3$ (max dose 2.25 g/day) in 59 ESRD patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) treatments. The study consisted of 2 weeks washout, 4 weeks dose titration, and 4 weeks placebo controlled evaluation period. Patients with serum Pi > 3.0 mmol/L (9.3 mg/dL) were excluded. At the end of the dose titration, 70% of patients had serum Pi \leq 1.8 mmol/L (5.6 mg/dL) with 64.7% of $\text{La}_2(\text{CO}_3)_3$ –treated patients maintaining Pi control versus 21.4% of placebo group. Mean lanthanum concentration was 0.67 ± 0.98 ng/g and 0.14 ± 0.26 ng/g in the La and placebo groups, respectively. Using an identical study design, Chiang *et al.* ^[80] have recently reported results similar to the above study in 73 Chinese patients with end stage renal disease. Serum Pi levels \leq 1.8 mmol/L (\leq 5.6 mg/dL) were observed in 60% of $\text{La}_2(\text{CO}_3)_3$ –treated patients compared to 10% of the placebo group ^[80].

Previous studies in rats with chronic renal failure had indicated that $\text{La}_2(\text{CO}_3)_3$ might affect bone formation. However, subsequent studies, using lanthanum doses up 1000 mg/kg in rats with normal renal function and in 5/6th nephrectomized rats showed no effect of lanthanum on osteoblasts, leading to the conclusion that decreased bone formation was a result of Pi depletion and Pi mobilization from bone ^[81]. Behets *et al.* ^[82] studied the effect of $\text{La}_2(\text{CO}_3)_3$ on bone morphology in 5/6th nephrectomized rats. Thirty-one animals received oral $\text{La}_2(\text{CO}_3)_3$ (2000 mg/kg/day). Six animals received the vehicle. Bone lanthanum distribution and bone histomorphometry were performed after 12 weeks of treatment. Lanthanum was localized to the edge of mineralized bone, regardless of the

type of bone turnover. There was no correlation between lanthanum and the presence of osteoid or the underlying bone pathology^[82]. The findings suggest that lanthanum deposition in bone is not associated with defective mineralization.

D'Haese *et al.*^[63] evaluated bone changes in 98 dialysis patients treated with $\text{La}_2(\text{CO}_3)_3$ or CaCO_3 (1:1 ratio). Bone changes were assessed by performing bone biopsies at baseline and after one year of treatment. $\text{La}_2(\text{CO}_3)_3$ resulted in improvements in the majority of bone biopsy parameters studied. At the end of the study, low turnover bone disease or hyperparathyroidism were present in 53% of CaCO_3 -treated patients compared to 18% of the lanthanum-treated patients. Mean plasma lanthanum levels were 0.51 to 1.08 $\mu\text{g/L}$ (3.67 – 7.78 nmol/L). Median bone lanthanum concentration was 1.8 $\mu\text{g/g}$ wet weight^[63].

In a randomized, controlled, open label trial, $\text{La}_2(\text{CO}_3)_3$ was compared to CaCO_3 in 800 ESRD patients (533 on $\text{La}_2(\text{CO}_3)_3$ and 267 on CaCO_3). After 1-3 weeks washout, those patients with serum Pi levels ≥ 5.58 mg/dL (≥ 1.8 mmol/L) entered a 5-week dose titration phase, followed by 20-weeks maintenance treatment. The median dose required for phosphate control was 2250 mg for $\text{La}_2(\text{CO}_3)_3$ and 3000 mg for CaCO_3 ^[83]. Average baseline serum Pi was ~ 8.3 mg/dL (2.68 mmol/L) for both groups. Serum Pi concentrations decreased to 5.79 ± 1.61 mg/dL (1.87 ± 0.5 mmol/L) in the lanthanum group and to 5.15 ± 1.49 mg/dL (1.66 ± 0.48 mmol/L) in the CaCO_3 group. Serum Pi was controlled in 67.9% of lanthanum-treated patients compared to 65.8% of CaCO_3 -treated patients. $\text{La}_2(\text{CO}_3)_3$ treatment resulted in lower Ca x Pi product ($p = 0.061$ at week

25). Clinically significant hypercalcemia was observed in 20.2% of patients receiving CaCO_3 and in 0.4% of patients receiving $\text{La}_2(\text{CO}_3)_3$.

In a one-year extension study to assess the safety of $\text{La}_2(\text{CO}_3)_3$, 143 patients participating in two short-term studies^[77, 78, 84] were continued for 52 weeks on the $\text{La}_2(\text{CO}_3)_3$ dose found to be effective^[84]. The dose was adjusted throughout the study to maintain serum Pi ≤ 5.9 mg/dL (≤ 1.9 mmol/L). Serum Pi levels were controlled in 53% of the patients. Mean serum Pi at the end of the study was 5.7 ± 1.4 mg/dL (1.84 ± 0.5 mmol/L) and had remained in this range since week 4. Mean plasma lanthanum concentrations remained unchanged (0.8 ± 1.0 ng/mL at week 6 and 0.5 ± 0.7 ng/mL at week 52). There were no significant changes in serum calcium concentration, Ca x Pi product, or serum PTH. The most common adverse events were nausea (26%), peripheral edema (23.4%), and myalgia (20.8%). No treatment-related serious adverse events were observed.

In another long-term study, hemodialysis patients were maintained on $\text{La}_2(\text{CO}_2)_3$ or on calcium-based phosphate binders. The interim analysis included 616 patients receiving lanthanum and 612 patients receiving standard therapy with 98 patients having completed 2 years of treatment^[84]. Serum Pi was controlled equally well with lanthanum and with conventional Pi binders.

Preliminary results show that $\text{La}_2(\text{CO}_3)_3$ is well tolerated for up to 2 years, with lower incidence of hypercalcemia compared to calcium-based Pi binders^[85]. Mortality was lower in $\text{La}_2(\text{CO}_3)_3$ -treated patients compared to standard therapy (12% versus 5.1%).

Since this analysis was based on a small portion of the enrolled patients, any conclusions on the effect of $\text{La}_2(\text{CO}_3)_3$ on mortality should await the completion of the studies.

In summary, $\text{La}_2(\text{CO}_3)_3$ is a newly approved calcium- and aluminum-free Pi binder which has been shown to be as effective as CaCO_3 with significantly lower incidence of hypercalcemia. Its therapeutic effect is limited to the control of Pi absorption with no effect on serum lipids. In clinical trials, $\text{La}_2(\text{CO}_3)_3$ was well tolerated with adverse events similar to placebo. The systemic absorption of $\text{La}_2(\text{CO}_3)_3$ appears to be extremely low with no evidence of accumulation in long-term studies. Unlike aluminum, the use of lanthanum has not been associated with low turnover bone disease or with neurological complications. Further long-term safety follow-up may be necessary to determine if chronic low-level exposure to lanthanum could result in any adverse health consequences.

New lanthanum-derived phosphate binders

Several new lanthanum-based compounds are in early stages of development.

Lanthanum dioxycarbonate (RenaZorb, Altair Nanotechnologies, Reno, NV) is reported to bind phosphate more efficiently and to be more insoluble than unmodified $\text{La}_2(\text{CO}_3)_3$, which could potentially reduce lanthanum absorption by the gastrointestinal tract^[86].

Altair has already obtained successful results for phosphate binding in dogs, rats and 5/6th nephrectomized rats. Based on *in vitro* studies, RenaZorb has higher phosphate-binding capacity and, therefore, lower doses may be required to achieve similar binding to existing Pi binders^[87]. Spectrum Pharmaceuticals, Inc (Irvine, CA) has signed a

licensing agreement to further develop this agent for clinical use ^[88]. Animal studies are currently underway to confirm proof of concept. Because this information was reported only through news release, one must await scientific reports of the final experimental results to evaluate the advantages of these new compounds.

Colestimide

Colestimide, also known as MCI-196 or colestilan is a nonabsorbable anion exchange resin, which lowers serum cholesterol by its ability to bind and sequester bile acids. It has been used in Japan for the treatment of hyperlipidemia ^[89]. It was discovered that colestimide could lower serum phosphorus concentrations when administered to dialysis patients ^[90]. Subsequent studies showed that colestimide has a high capacity to bind phosphate. In *in vitro* experiments, one gram of the compound binds 2.52 mmol Pi at pH 7.2. ^[91], which is very close to the Pi binding capacity reported for sevelamer HCl (see table 1). Colestimide decreases urinary Pi excretion when administered to rats or in healthy volunteers ^[91]. Date *et al.* ^[90], performed an uncontrolled open label study of 28 hemodialysis patients with hyperphosphatemia, not adequately controlled with CaCO₃ (average dose = 3.5 g/day). Colestimide was added for 4-weeks at a dose of 3 g/day and CaCO₃ was continued. In 13 subjects, the dose had to be reduced to 1.5 g/day due to constipation. Serum Pi decreased from 6.1 ± 1.1 mg/dL to 5.5 ± 1.2 mg/dL (1.97 ± 0.25 mmol/L to 1.78 ± 0.39 mmol/L) at 2 weeks and remained under control at 5.3 ± 1.1 mg/dL (1.71 ± 0.35 mmol/L) at 4 weeks (p <0.0001). Serum calcium levels were not altered but Ca x Pi product decreased from 59.6 ± 11.3 mg²/dL² to 50.5 ± 12 mg²/dL² after 4 weeks (p <0.0001). Serum TC levels also decreased from 157 ± 26 mg/dL (4.07 ±

0.67 mmol/L) at baseline to 134 ± 25 mg/dL (3.47 ± 0.65 mmol/L) after 2 weeks.

Because of its uncontrolled design, the results of this study must be interpreted with caution. However, they provide proof of concept that colestimide, prescribed at clinically acceptable doses, has the ability to reduce serum Pi concentrations in ESRD patients.

Kurihara *et al.* ^[91] performed a short-term randomized, double-blind, placebo controlled study of colestimide (MCI-196) in 79 Japanese HD patients. After a 2-week washout, those patients whose serum Pi was ≥ 6.5 mg/dL (≥ 2.1 mmol/L) were randomized to receive the active drug or placebo for 2 weeks. Colestilan was prescribed to 33 subjects at a dose of 6 g/day. There was a significant reduction in mean serum Pi concentration (-0.55 ± 1.23 mg/dL) (-0.18 ± 0.40 mmol/L) in colestilan-treated patients but an increase in mean serum Pi concentration ($+0.84 \pm 0.95$ mg/dL) ($+0.27 \pm 0.31$ mmol/L) in the placebo group ($p = 0.002$). Adverse reactions, mainly gastro-intestinal and including constipation, were observed in 51.7 % of colestilan-treated patients and 29.4% of placebo-treated patients. Because serum Pi levels remained significantly above the recommended goal of ≤ 5.5 mg/dL (≤ 1.78 mmol/L), longer treatment durations coupled with dose titration would be required to achieve lower serum Pi levels. TC and LDL-C levels decreased on average -35.2% and 32.2%, respectively, while there were no significant changes in the placebo group. Colestilan-treated subjects showed a mild degree of hyperchloremic metabolic acidosis. This short-term study supports further development of colestilan as a Pi binder in patients with end-stage renal disease. Whether higher doses could be safely administered will also require further investigation.

Given that the drug is already approved for use as a bile acid sequestrant, its further development as a Pi binder could be accelerated.

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Table I. Major properties of new phosphate binders

Name	Specific properties	Pi binding capacity (<i>in vitro</i> or <i>in vivo</i>)	Other characteristics	Reference
CaCO ₃ (reference)	Binds Pi by physiochemical reaction	1.26 mmol Pi/g compound	No binding at pH <3. Can cause hypercalcemia. Inexpensive	3, 75
Calcium acetate (PhosLo)	Binds Pi by physiochemical reaction	1.45 mmol Pi/g compound	Can cause hypercalcemia. Moderately expensive	3, 75
Sevelamer HCl (RenaGel)	Polymer resin: binds Pi by ion exchange and hydrogen bonding	2.5-2.7 mmol Pi/g compound at 5 mM Pi	Ca ⁺⁺ -free. Not absorbed. Lowers TC, LDL-C. No change or ↑ in HDL-C Very expensive	27
Lanthanum carbonate (Fosrenol)	Binds Pi by physiochemical reaction	1.34 to 2.68 mmol/g compound at 2-4 mM Pi, pH =7	Ca ⁺⁺ - free. Poorly absorbed. 99.9% bound to plasma proteins. Expensive	73
MCI-196 (colestilan or colestimide)	Anion exchange resin: binds Pi by ion exchange	2.52 mmol Pi/g compound at 2-4 mM Pi, pH 7.2	Ca ⁺⁺ -free. Can lower LDL-C and TC. Not approved as a Pi binder	61

Information on CaCO₃ and calcium acetate is given as reference. Data compiled from various sources listed in reference column, and especially from Baxter J, *et al.* J Pharm Pharmacol 2000; 52: 863-874 (Ref 92) with permission from the Journal of Pharmacy and Pharmacology (Pharmaceutical Press) and from Loghman-Adham M. Drug Safety 2003; 26 (15): 1093-1115 (Ref 8) with permission of Adis International.

Table II. Summary of human studies with phosphate binders in development or recently approved

Compound	Study design	Results summary	Author/Ref
Ca α -ketoglutarate	Open label uncontrolled study. Ca-KG 4.5 g/day for 36 months in 14 HD patients.	Serum Pi decreased from a baseline of 2.6 ± 0.1 mmol/L to 1.9 ± 0.07 mmol/L. Slight increase in serum Ca to 2.47 mmol/L	93
Ca α -ketoglutarate	Randomized cross-over trial. 19 HD patients, 12 weeks treatment. Comparison of Ca-KG and CaCO ₃ .	Serum Pi decreased from 1.7 ± 0.06 mmol/L at baseline to 1.45 ± 1.0 mmol/L. Lower daily calcium load and lower mean plasma Ca with Ca-KG than with CaCO ₃ . Severe GI problems in 5 pts	25
Ca α -ketoglutarate	Randomized cross-over study in 28 HD patients, 4 week treatment. Ca-KG versus Ca acetate used at equivalent Ca doses	Serum Pi decreased from 2.47 ± 0.63 mmol/L at baseline to 1.95 ± 0.4 mmol/L at 4-wks. Lower incidence of hypercalcemia with Ca-KG. Ca-KG was well tolerated	24
Lanthanum carbonate	LAM-302 study. Randomized placebo-controlled, parallel group. 126 HD patients. 3-wk washout, 6-wk dose titration, 4-wk maintenance.	Serum Pi < 1.93 mmol/L in 59% of controls vs 23% of placebo-treated pts. Maximum La ₂ (CO ₃) ₃ dose 3 g/day. Mean difference in serum Pi between La ₂ (CO ₃) ₃ and placebo was 1.91 mg/dL (0.62 mmol/L) (p<0.0001).	78
Lanthanum carbonate	Placebo-controlled double-blind dose finding study, using 0.225 to 2.25 g La for up to 6 weeks. 145 stable HD patients.	Dose-dependent decrease in serum Pi levels. Blood La levels increased with increasing La ₂ (CO ₃) ₃ dose (1.16 ± 1.91 ng/ml at 2.25 g dose). Adverse events (nausea and vomiting) seen in 39% of La ₂ (CO ₃) ₃ and in 44% of placebo groups	77
Lanthanum carbonate	Randomized open label, controlled trial of 800 patients comparing La ₂ (CO ₃) ₃ and CaCO ₃ (3:1 ratio). 1-3 wk washout, 5-wk dose titration, 20-wk maintenance	Median daily dose 2.25 g. Lower Ca x Pi with La ₂ (CO ₃) ₃ . Pi control achieved in ~ 65% of patients in both groups. Hypercalcemia seen in 0.4% of La ₂ (CO ₃) ₃ and 20.2% of CaCO ₃ -treated patients. La ₂ (CO ₃) ₃ was well tolerated	83
Lanthanum carbonate	One-year open label extension from 2 previous short-term efficacy studies. 143 patients, who had completed 8 weeks and 10 weeks of treatment with La ₂ (CO ₃) ₃ .	Most common adverse events: nausea (26%), peripheral edema (23.4%), myalgia (20.8%). No treatment-related SAEs. Mean serum Pi 5.7 ± 1.4 mg/dL (1.84 ± 0.5 mmol/L). Pi levels controlled in 53% of patients. No significant changes in serum Ca or serum PTH	84
Lanthanum carbonate	Long-term controlled trial of safety and efficacy of La ₂ (CO ₃) ₃ in HD patients. Interim analysis included 616 of La ₂ (CO ₃) ₃ - treated patients and 612 on standard therapy.	Equal control of serum Pi with both treatments. Twice as many deaths in the conventional treatment group as in La ₂ (CO ₃) ₃ group. 98 patients completing 2-years of treatment.	84
Lanthanum carbonate	Randomized controlled trial of efficacy of La ₂ (CO ₃) ₃ (max dose 2.25 g/day). 59 HD and CAPD patients. 2-wk washout, 4 wk dose titration, 4 wk placebo control. Patients with serum Pi > 3.0 mmol/L were excluded.	At the end of dose titration 70% of patients had serum Pi ≤ 1.8 mmol/L with 64.7% La ₂ (CO ₃) ₃ -treated patients and 21.4% of placebo group maintaining Pi control. La concentration was 0.67 ± 0.98 ng/g and 0.14 ± 0.26 ng/g in the La and placebo groups, respectively	79

Compound	Study design	Results summary	Author/Ref
Sevelamer HCl	Randomized placebo-controlled double blind trial. 36 HD pts. 2-week baseline, 2-week washout, 2-week evaluation	Serum Pi declined 0.38 mmol/L with sevelamer and increased 0.06 mmol/L with placebo. Better results in compliant pts Reduced TC and LDL-C with sevelamer	35
Sevelamer HCl	Dose titration study. 48 HD patients, receiving 1.5 - 4.5 g sevelamer /day for 8 weeks. Dose escalation every 2-weeks.	Serum Pi nadir of 2.1 mmol/L reached at 7 weeks. PTH levels declined. Reductions in TC and LDL-C of 23% and 35.9%, respectively	37
Sevelamer (RenaGel)	HD patients, dose titration study. 15 patients; 2-week washout, 8-week study	Serum Pi fell by 4.5 mg/dL at the end of titration period. 23% fall in TC and 35.9% fall in LDL-C. HDL-C and fat-soluble vitamins not affected	38
Sevelamer HCl	Open label dose titration, 172 HD patients. 2-week washout, 8 week treatment	Serum Pi declined from 2.94 ± 0.77 to 2.1 ± 0.6 mmol/L. Lower serum PTH after sevelamer despite low serum Ca (2.35 ± 0.22 mmol/L). Reduced serum TC and LDL-C	36
Sevelamer	Open label, 192 HD patients on Alu or Ca-based binders for >1 mo. Subjects had completed a dose titration study. 2-week washout. 3 dose ranges. Total duration 46 wks. Mean prescribed dose 6.3 g/day	Mean Δ Serum Pi -0.71 ± 0.77 mmol/L Mean Δ Ca x Pi -1.46 ± 1.78 mmol ² /L ² LDL-C decreased 30% HDL-C increased 18%	39
Sevelamer HCl	Open label cross-over study comparing sevelamer to Ca acetate. 84 HD patients, 2-week washout, 8 week treatment periods	Mean change in serum Pi from baseline was identical for the two treatments (~ 0.65 mmol/L). Serum Ca increased with both treatments, but more with calcium acetate (0.2 vs 0.7 mg/dL). Hypercalcemic episodes were lower with sevelamer (5% vs 22%)	42
Sevelamer HCl	Open label, uncontrolled study in 17 children (14 PD, 3 HD) aged 2-17 years previously on Ca-based Pi binders. 2-wk washout, 6-mo treatment with sevelamer (mean dose 6.7 ± 2.4 g/day)	Serum Pi declined compared to baseline and stable from 8-wks to the end of study. Pi control sub-optimal despite high doses. Serum Ca unchanged from baseline. Ca x Pi lower at study end.	41
Sevelamer HCl	Randomized multicenter parallel design: sevelamer vs Ca acetate or CaCO ₃ . 200 HD patients: 12 week dose titration; dose escalation every 3 weeks to achieve target serum Pi and Ca. EBT imaging at 0, 26, 52 weeks.	Equivalent control of serum Pi with all treatments. Serum Ca higher with Ca binders than sevelamer (16% vs 5%). Median % change in Ca scores in coronary arteries and aorta were lower in sevelamer-treated vs Ca binder-treated Pts (p=0.02).	45
Sevelamer HCl	Open label, randomized parallel design study 108 HD patients receiving Ca acetate or sevelamer. 2-wk washout, 12 weeks dose titration. Total duration 52 weeks. Ca deposition in arteries determine by EBT	Equivalent reduction of serum Pi with both treatments. More frequent hypercalcemia (sCa ≥ 10.5 mg/dL) in Ca acetate treated subjects (36% vs 13%). Ca acetate was associated with increased calcification in coronary arteries and in the aorta. No significant change in calcification in sevelamer-treated subjects	47
Sevelamer HCl	Study based on 108 US participants of treat-to-goal study (above). Assessments for TC, LDL-C, HDL-C, at 12, 24, and	Average sevelamer dose = 6.5 ± 2.9 g/day; average Ca acetate dose = 4.3 ± 2.2 g/day. Changes in coronary artery Ca scores as above.	49

Compound	Study design	Results summary	Author/Ref
	52 weeks. hs-CRP, homocysteine, β_2 -microglobulin measured at baseline and at 52 weeks.	Significant decreases in hs-CRP, β_2 -microglobulin, TC, LDL-C and apolipoprotein B and significant increase in HDL-C in sevelamer-treated patients. No changes in the same parameters in calcium acetate-treated patients.	
Sevelamer & Ca acetate	Randomized, double blind study of 98 HD patients receiving either Ca acetate or sevelamer for 8 weeks. 1-3 wks washout to reach serum Pi \geq 6.0 mg/dL; 8-wks treatment. Starting dose based on serum [Pi] after washout.	Ca acetate-treated patients had lower serum Pi and lower Ca x Pi product. but higher serum Ca concentrations ($\Delta=0.63$ mg/dl ($p<0.0001$)). Metabolic acidosis seen in patients on sevelamer: Serum bicarbonate 21.0 ± 2.6 mEq/L for Ca acetate and 19.3 ± 2.7 mEq/L for sevelamer.	48
Sevelamer HCl	Interventional study: 25 dialysis patients, continued on previous Pi binders. Sevelamer added in addition. 3-mo baseline without sevelamer, 3-mo titration, 3-mo maintenance	Mean Pi conc. decreased from 2.11 ± 0.06 mmol/L (6.6 ± 0.2 mg/dL) to 1.91 ± 0.01 mmol/L (5.9 ± 0.003 mg/dL) No change in serum Ca or in PTH levels. Ca x Pi product was decreased. Average sevelamer dose = 2.4 g/day. Elemental calcium intake declined from 3.4 to 1.3 g/day.	61
Colestimide	Uncontrolled, open label study. 28 HD patients continued on CaCO_3 (mean dose 3.5 ± 1.1 g/day), also started on colestimide (3 g/day) for 4 wks.	Colestimide dose reduced to 1.5 g/day in $\frac{1}{2}$ the patients due to constipation (mean dose 2.3 ± 0.8 g). Serum Pi decreased from 6.1 ± 1.1 to 5.5 ± 1.2 mg/dL ($p<0.0001$). No change in serum Ca. Effect on Pi difficult to interpret due to combination and lack of controls	90
MCI-196 (colestilan)	Randomized, double-blind, placebo controlled. 79 Japanese HD patients (33 received MCI). 2-wk washout, 2-wk treatment (6 g/day).	Change in serum -0.55 ± 1.23 mg/dL for MCI-196 and $+0.84 \pm 0.95$ mg/dL for placebo ($p = 0.002$). Adverse reaction, GI symptoms, constipation in 51.7% of patients.	91

Ca-KG: Calcium alpha ketoglutarate; $[\text{La}_2(\text{CO}_3)_3]$: lanthanum carbonate; HD: hemodialysis; EBT: Electron beam tomography scan; PTH: parathyroid hormone; CKD: chronic kidney disease. hs-CRP: high sensitivity C-reactive protein

Table III. Comparison of cost of different phosphate binders

Brand name	Cost for 100 tablets/capsules (highest strength)	Price expressed as percent of RenaGel price
RenaGel (sevelamer HCl)	\$189.00	100.00
Fosrenol (lanthanum carbonate)	\$132.49	70.10
PhosLo (calcium acetate)	\$21.59	11.42
Oscal (calcium carbonate)	\$13.15	6.96
Tums (calcium carbonate)	\$3.33	1.76

Prices calculated from information available at Sav-Rx prescription services (reference 94).

Figure legends

Figure 1. Relationship between GFR and urinary Pi excretion.

The nomogram is based on hypothetical data calculated, using 80% tubular reabsorption of Pi. Twenty-four hour urinary Pi excretion is shown on the right hand y axis and different GFR values are marked next to the converging lines. Each line represents changes in urinary Pi excretion as a function of changes in serum Pi concentration (x axis). As serum Pi concentration increases, the filtered load of Pi will increase, allowing more Pi to be excreted. However, if the GFR is reduced (e.g. below 30 ml/min), the filtered load of Pi and the amount of Pi excreted will be markedly reduced, as shown by less steep lines for lower GFR values. The calculated values do not take into consideration increased excretion of Pi in stools and down-regulation of Na⁺-Pi cotransporters as a result of increased serum Pi concentration.

To convert Pi concentration from mg/dL to mmol/L, multiply by 0.323. For calcium, to convert mg/dL to mmol/L, multiply by 0.25.

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Fig. 1

