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Safety of New Phosphate Binders for Chronic Renal Failure

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Contents

Abstract

Phosphate (Pi) retention is a common problem in patients with chronic kidney disease, particularly in those who have reached end-stage renal disease (ESRD). In addition to causing secondary hyperparathyroidism and renal osteodystrophy, recent evidence suggests that, in ESRD patients, high serum phosphorus concentration and increased calcium and phosphorous (Ca × P) product are associated with vascular and cardiac calcifications and increased mortality. Dietary phosphorus restriction and Pi removal by dialysis are not sufficient to restore Pi homeostasis. Reduction of intestinal Pi absorption with the use of Pi binders is currently the primary treatment for Pi retention in patients with ESRD. The use of large doses of calcium-containing Pi binders along with calcitriol administration may contribute to over-suppression of parathyroid hormone secretion and adynamic bone disease as well as to a high incidence of vascular calcifications. When used in patients with impaired renal function, aluminium salts were found to

accumulate in bone and other tissues, resulting in osteomalacia and encephalopathy.

Sevelamer, an aluminium- and calcium-free Pi binder can reduce serum phosphorus concentration and is associated with a significantly lower incidence of hypercalcaemia, while maintaining the ability to suppress parathyroid hormone production. An additional benefit of sevelamer is its ability to lower low density lipoprotein-cholesterol and total cholesterol levels. Sevelamer attenuates the progression of vascular calcifications in haemodialysis patients, which may lead to lower mortality. The use of sevelamer in non-dialysed patients might aggravate metabolic acidosis, common in these patients. Several other calcium-free Pi binders are in development. Lanthanum carbonate has shown significant promise in clinical trials in ESRD patients. Magnesium salts do not offer a significant advantage over currently available Pi binders. Their use is restricted to patients receiving dialysis since excess magnesium must be removed by dialysis. Iron-based compounds have shown variable efficacy in short-term clinical trials in small numbers of haemodialysis patients. Mixed metal hydroxyl carbonate compounds have shown efficacy in animals but have not been studied in humans. Major safety issues include absorption of the metal component with possible tissue accumulation and toxicity.

The concentration of phosphorus in normal human serum is maintained between 3.5 and 4.5 mg/dL (1.2–1.45 mmol/L). Phosphate (Pi) homeostasis is achieved primarily by the kidneys and to a lesser degree by the intestine.[1,2] In end-stage renal disease (ESRD), Pi retention occurs because of the inability of the diseased kidneys to increase Pi excretion to match the intake. Pi retention is associated with a number of complications including secondary hyperparathyroidism and renal osteodystrophy,[3-5] increased mortality,[6,7] and accelerated progression of renal failure.[8,9]

In experimental animals, reducing phosphorus intake in proportion to the reduction in glomerular filtration rate (GFR) prevents Pi accumulation and its consequences.[8,10] In clinical practice, however, this is difficult to achieve because phosphorus is present in all major food groups making strict adherence to a low phosphorus diet impractical.[1] A direct relationship exists between protein and phosphorus content in food.[11] To maintain adequate nutritional balance, protein intake must be maintained around 1.2 g/kg/day in stable haemodialysis patients and up to 1.3 g/kg/day in peritoneal dialysis patients.[12] To provide this amount of protein, phosphorus intake will have to be >1000 mg/day, far above the capacity of standard thrice weekly dialysis to remove.[11] The use of Pi binders, therefore, has been necessary in patients with advanced kidney disease not yet on dialysis and in those requiring standard haemodialysis or peritoneal dialysis.

The average dietary phosphorus intake is 1000–1200 mg/day, of which about 60% is absorbed. Therefore, 600–700mg of Pi must be excreted in 24 hours to maintain Pi homeostasis. As the GFR decreases to levels <20 mL/min, it becomes difficult for the urinary Pi excretion to match the dietary phosphorus intake. Assuming that 600mg of Pi is absorbed daily, to maintain Pi balance at a GFR of 30 mL/min, the serum phosphorus concentration would have to increase to >7 mg/dL (>2.26 mmol/L), whereas it would remain <4 mg/dL (<1.3 mmol/L) when the GFR is 50 mL/min (figure. 1). As the GFR declines further, dietary phosphorus restriction alone will not be sufficient to maintain Pi balance, even after starting haemodialysis. Assuming a phosphorus intake of 900 mg/day (30% reduction), weekly Pi removal of 2700mg (900mg per 4-hour session) by dialysis, and daily urinary Pi excretion of 100mg (see figure 1 for GFR ≤10 mL/min), the weekly Pi balance will be +380mg. Accordingly, in both chronic kidney disease (CKD) patients and in patients on dialysis, dietary phosphorus restriction and the use of Pi binders will be necessary to reduce

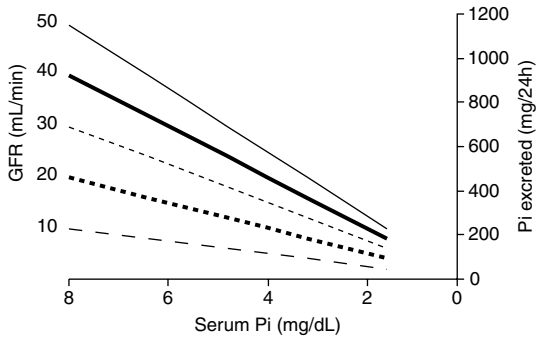

Fig. 1. Relationship between glomerular filtration rate (GFR) and urinary phosphate (Pi) excretion. The nomogram is based on hypothetical data calculated, using 80% tubular reabsorption of Pi. Twenty-four hour urinary Pi excretion is shown on the right-hand y axis and different GFR values are marked 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. <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 sodium (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.

the filtered load of Pi and return the serum phosphorus concentrations toward normal.

Currently, the most widely used Pi binders are calcium salts including calcium carbonate and calcium acetate.[13-15] Hypercalcaemia remains a frequent problem when calcium-based Pi binders are used. There is evidence of an association between elevated serum Pi concentration or calcium and phosphorous (Ca × P) product and increased mortality in patients receiving haemodialysis.[7] When used in patients with impaired renal function, aluminium salts were found to accumulate in bone and other tissues, resulting in osteomalacia and encephalopathy. Recent efforts, therefore, have focused on the development of Pi binders devoid of calcium and aluminium. The only calcium- and aluminium-free Pi binder currently approved in the US and Europe is sevelamer. Several other compounds are in various stages of development. All Pi binders currently in development are based on metal ions, which could lead to possible absorption and accumulation of the metal component. The long-term consequences of accumulation of some metals on patient safety remains unknown.[16,17]

Phosphate retention and its consequences could be treated, in principle, by several methods (table I). Extracellular volume expansion and diuretics can increase urinary Pi excretion but are not practical or effective in CKD. Specific inhibitors of intestinal sodium (Na^+)-Pi cotransporter are in the early stages of development. Some non-calcaemic vitamin D analogues (e.g. paricalcitol) can also result in less phosphorus absorption which, combined with reduced risk of hypercalcaemia, is beneficial in patients treated with calcium-containing Pi binders.[18,19] Calcimimetics are a new class of compounds that selectively activate the calcium receptor on the parathyroid glands.[20] Cinacalcet (AMG 073) is a new calcimimetic agent that, in addition to inhibiting parathyroid hormone (PTH) secretion, was shown to reduce serum phosphorus concentrations.[21]

In this review, Pi removal by dialysis and the possible role of Pi transport inhibitors in preventing

Table I. Methods for prevention of hyperphosphataemia (reproduced from Loghman-Adham,[22] with permission from Springer-Verlag GmbH & Co. KG)

Low phosphorus diet
Reduction of intestinal Pi absorption
Pi binders
Calcium salts: calcium carbonate, calcium acetate, calcium α-ketoglutarate
Calcium-free binders: sevelamer, lanthanum carbonate
Inhibitors of intestinal Na^+-Pi cotransport
2′-phosphophloretin[a]
Niceritrol
Phosphate removal by dialysis
Non-calcaemic vitamin D analogues
Paricalcitol[b]
Increased renal Pi excretion
Inhibitors of renal Na^+-Pi cotransport[a]
Diuretics, ECF volume expansion[c]
Calcimimetic agents
Cinacalcet (AMG 073)[b]

a Not tested in humans.

b Vitamin D analogues and calcimimetics also reduce PTH production, leading to reduced Ca × P product.

c Diuretics are of limited use in end-stage renal disease.

Ca = calcium; **ECF** = extracellular fluid; **Na** = sodium; **Pi** = phosphate; **PTH** = parathyroid hormone.

Pi absorption will be briefly discussed. To help understand the need to develop new Pi binders, the aluminum- and calcium-based Pi binders will be reviewed. A detailed review of sevelamer, a recently approved aluminium- and calcium-free Pi binder will also be provided. This will be followed by a review of new Pi binders still in development. Where no human data exists, the available animal data will be described. Throughout this review, the primary emphasis will be on the discussion of the safety of Pi binders.

1. Phosphate (Pi) Removal by Haemodialysis

Pi removal by haemodialysis shows a weak correlation with Kt/V, a standard measure of dialysis adequacy based on dialyzer urea clearance at prescribed blood and dialysate flow (K), prescribed treatment time (t), and the urea distribution volume (V),[23] suggesting that other factors may also affect Pi removal during dialysis. The kinetics of Pi removal during haemodialysis are biphasic, following a two-compartment model: there is a rapid initial removal from the extracellular compartment followed by a much slower removal, mainly due to Pi efflux, from the intracellular to the extracellular compartment.[24-28] After the completion of dialysis, a rebound phenomenon is observed with serum phosphorus concentrations increasing between 30 and 40% within 1 hour.[29,30] The Pi rebound is more pronounced when acetate is used as buffer compared with bicarbonate.[29,31]

In theory, Pi removal during dialysis could be modified by various manoeuvers:

1. Increasing dialysis time can improve Pi removal.[28,32] Conventional haemodialysis removes approximately 930mg (30 mmol) of Pi during a 4-hour session.[33] Assuming a dietary phosphorus intake of 1000 mg/day and 50% intestinal Pi absorption, Pi balance could be achieved by performing 2 hours 40 minutes of dialysis five times a week (800 minutes) or 5 hours 30 minutes of dialysis three times a week (990 minutes).[32,34] In reality, intestinal Pi absorption is closer to 60% and can further increase in patients receiving oral calcitriol.[32]

2. Increasing the dialyzer surface area can also increase Pi removal,[29,32,35] but the type of dialysis membrane does not appear to have an effect.[29,36]

3. Haemofiltration is somewhat more effective in removing Pi than standard haemodialysis.[37]

4. Potassium-free dialysate fluids can increase Pi removal by enhancing Pi efflux from the intracellular compartment.[32,38] However, this manoeuver can be risky in some patients and remains experimental.

5. Acidifying the dialysate fluid can result in increased efflux of Pi from the intracellular compartment, leading to increased removal by dialysis.[39] This method has not been effective in all studies.[40] An undesirable adverse effect of acidification is that it could increase Pi rebound at the end of dialysis.[29] Except for increased dialysis time and the use of dialyzers with larger surface area, no other method is currently used in clinical practice, due to lack of clear benefit and possible risks associated with their use.

Using kinetic modelling, Gutzwiller et al.[23] showed that with high flux haemodialysis, 1128 ± 15mg (36.4 ± 0.5 mmol) of Pi is removed in 5 hours, compared with 923 ± 12mg (29.8 ± 0.4 mmol) in 4 hours.[23] Because of improved metabolic control, short hemeral (daily) haemodialysis and nocturnal haemodialysis have been advocated.[41,42] Most studies have shown improved phosphorus control, allowing relaxation of nutritional restrictions and even cessation of Pi binders.[30,42-44] A large number of patients even require Pi supplements.[44,45] Long-term experience with these methods is limited but a few patients have been successfully managed for up to 5 years at selected centres.[41,45]

2. Modifying Pi Excretion and/or Intestinal Absorption

Marked similarities exist between the molecular mechanisms of Pi transport across the brush border membrane (BBM) of the enterocyte and the renal proximal tubule.[46] The Na^+-Pi cotransporter proteins for both sites belong to the type II Na^+-Pi cotransporters. The NaPi-2a or sodium-dependent phosphate cotransporter type 2 (NPT2 in humans) is present only in renal BBM, while NaPi-2b is present in the BBM of the small intestine and in the lungs.[46] Phosphonocarboxylic acids can inhibit Pi transport

at both sites and can induce phosphaturia when injected acutely into rats.[47] Phosphonoformic acid administered orally for 8 weeks to five-sixth nephrectomised rats, caused increased urinary Pi excretion but no significant reduction in plasma Pi concentrations.[47] Phosphonoformic acid is a relatively weak inhibitor of Na^+-Pi cotransport (Ki [inhibitory constant] approximately 0.5 mmol/L).[48] The intravenous injection of phosphonoformic acid has been associated with nephrotoxicity, electrolyte disturbances, penile ulcerations and seizures.[49] Phosphonoformic acid is, therefore, not suitable for human use as a Pi transport inhibitor. Other Pi transport inhibitors are currently in development and might lead to a new class of drugs in the treatment of hyperphosphataemia in CKD.

2.1 Phosphophloretin

A phosphorylated phloretin derivative, 2′-phosphophloretin, was shown to be a potent and specific inhibitor of Na^+-Pi cotransport in intestinal BBMs (50% inhibitory concentration [IC_{50}] approximately 55 nmol/L).[50] This compound reduced serum phosphorus concentrations by 45% when administered orally for 2 weeks to healthy rats (apparent *in vivo* $IC_{50} = 3$ μmol/L) without affecting serum glucose or calcium concentrations.[50] More potent inhibitors, therefore, are showing promising results as potential therapeutic agents.

2.2 Niceritrol

Niceritrol (pentaerythritol tetranicotinate), is a nicotinic acid derivative used in Japan and Europe for the treatment of hyperlipidaemia.[51] It was found to reduce serum phosphorus concentrations when administered to patients on haemodialysis.[52] In addition to its lipid-lowering effects, niceritrol can inhibit platelet aggregation.[53] Studies in healthy rats showed that oral administration of niceritrol for 4 days results in increased faecal Pi excretion without significant change in urinary Pi excretion.[54] Niceritrol is partially hydrolysed in the gut to nicotinic acid. Following absorption, various metabolites are produced which include nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP) and nicotinamide.[54] Intraperitoneal injections of nicotinamide into rats result in increased tissue NAD content, increased urinary Pi excretion and reduced renal BBM Na^+-dependent Pi transport.[55] It was also shown that nicotinamide injections can result in inhibition of Na^+-dependent Pi transport across the intestinal BBM.[56] Therefore, niceritrol might lead to inhibition of active Pi transport across both intestinal and renal BBMs, following hydrolysis or metabolic conversion to nicotinamide and increased tissue concentrations of NAD. This dual action might explain continued urinary Pi excretion despite reduced intestinal Pi absorption in rats treated with niceritrol.[54] Facial flushing occurs during the early stages of treatment and may be controlled with premedication with aspirin.[57] There has been a single case report of thrombocytopenia and anaemia in a patient on haemodialysis receiving niceritrol.[58] Considering the long-term clinical safety of this drug and its beneficial effects on the cardiovascular system, niceritrol may have a place in the treatment of hyperphosphataemia of CKD.

3. Aluminium-Based Pi Binders

Aluminium-containing salts are effective Pi binders and were used extensively until the mid-1980s. The gastrointestinal tract is a relatively impermeable barrier to aluminium[59] but under certain circumstances, sufficient aluminium can be absorbed to cause increased blood and tissue aluminium concentrations.[60] Excess aluminium is excreted by the kidneys so that aluminium intoxication is not observed in individuals with normal renal function.[59] When administered to patients with CKD, significant amounts of aluminium can be retained in the body, particularly in bones.[59,61] The gastrointestinal absorption of aluminium is higher in infants and children with CKD compared with adults.[62,63] It can also be enhanced by the concomitant use of citrate.[64-66] Aluminium accumulation can result in osteomalacia,[67,68] adynamic bone disease,[69] microcytic anaemia,[70-72] and encephalopathy.[59,73-75] The syndrome called dialysis encephalopathy was initially reported only in patients on haemodialysis and in many of them the source of aluminium was traced to contaminated water used to prepare the dialysate solutions.[76] Better water purification to remove aluminium was followed by a decline or disappearance of dialysis

encephalopathy. Subsequent reports indicated that encephalopathy could also occur when the only source of aluminium was gastrointestinal absorption from aluminium-containing Pi binders.[77-79] Aluminium accumulation has also been implicated in other neurodegenerative disorders such as Alzheimer's disease.[80] As a result of neurological complications, the use of aluminium salts has been limited to short periods in patients with difficult-to-control hyperphosphataemia.

4. Calcium-Based Pi Binders

4.1 General Considerations

During the past decade, calcium-containing salts have been the preferred Pi binders for use in patients with CKD. The effectiveness of high intake of calcium carbonate in reducing intestinal Pi absorption was first demonstrated >30 years ago by Clarkson et al.[81] Currently used calcium-containing Pi binders are calcium citrate, calcium carbonate, and calcium acetate. Although the available calcium salts are generally of good quality, a few formulation problems are worth discussing. Many generic and brand-name calcium salts were shown to have highly variable disintegration times under simulated gastric fluid (pH 1.5) or intestinal fluid (pH 7.5) testing conditions.[82] The relevance of these findings to *in vivo* activity remains to be determined. Another issue of particular concern in ESRD patients who require large doses of calcium-based Pi binders is the lead content of some calcium preparations.[83] Lead contamination has been observed with calcium carbonate but not with calcium acetate. Both natural products, such as oyster shell, and refined products have been shown to contain measurable amounts of lead.[83]

Iron absorption can be slightly reduced when iron is co-administered with calcium-based Pi binders.[84] Since the majority of haemodialysis patients receive parenteral iron, this should not cause a problem in most ESRD patients.

4.2 Calcium Citrate

Calcium citrate is an effective Pi binder capable of reducing plasma phosphorus concentrations and serum PTH concentrations.[85] The co-administration of calcium citrate with aluminium hydroxide gel was shown to cause a significant rise in plasma aluminium concentration and a 4-fold increase in urine aluminium excretion.[64,66] Calcium citrate increases aluminium solubility when added to aluminium chloride *in vitro*.[65,86] Citrate may further enhance aluminium absorption by increasing the paracellular transport of aluminium.[87] Due to its ability to enhance intestinal aluminium absorption and to higher the incidence of hypercalcaemia,[88] calcium citrate is rarely used as a Pi binder, but continues to be used as a calcium supplement.[89]

4.3 Calcium Carbonate

Following reports of aluminium toxicity with the use of aluminium salts as Pi binders, calcium carbonate became the only Pi binder available for use in both dialysis and predialysis patients.[15,90-93] Calcium carbonate is effective in reducing intestinal Pi absorption and in lowering serum phosphorus concentrations.[13,14,94-99] Contrary to calcium citrate, it does not increase aluminium absorption.[66] The Pi-binding capacity of calcium carbonate is maximal at pH 1.5. It is poorly soluble in neutral solutions and binds Pi poorly at neutral pH.[100] Gastric acid secretion is often impaired in patients with chronic renal failure (CRF) and many patients receive inhibitors of acid secretion.[101,102] Impaired gastric acidification may, therefore, reduce calcium carbonate dissolution and decrease its Pi-binding capacity.[103] The effect of inhibitors of gastric acid secretion on serum phosphorus concentrations, however, appears to be minimal.[104] The gastrointestinal solubility of calcium carbonate preparations can be variable and non-disintegrated tablets have been observed on abdominal x-rays.[105] Similarly, *in vitro* experiments testing the disintegration of 15 calcium carbonate formulations at pH 1.5 or 7.5, showed variable and unpredictable disintegration times in nine of the binders tested.[82]

Calcium carbonate has about half the Pi-binding capacity of calcium acetate.[13,95,100,106-110] In one study, the administration of calcium carbonate a few minutes before meals, instead of with meals, resulted in improved Pi-binding capacity.[111] This finding, however, could not be replicated. The incidence of hypercalcaemia, however, was lower when calcium carbonate was administered 5 minutes before

meals.[112] Hypercalcaemia is more common with calcium carbonate than with calcium acetate.[107,109] In patients receiving calcitriol, hypercalcaemia is seen with a similar frequency with both calcium carbonate and calcium acetate.[95,110,113] In patients reciving haemodialysis treatment, the use of a low calcium dialysate (2.5 mEq/L [1.25 mmol/L]) can significantly reduce the incidence of hypercalcaemia associated with calcium-based Pi binders.[114-117] Reducing dialysate calcium concentration might theoretically increase the risk of hyperparathyroidism [118] but increased PTH concentrations have not been reported when low calcium dialysate is used in conjunction with calcium carbonate.[115,119]

4.4 Calcium Acetate

Calcium acetate shares many therapeutic features with calcium carbonate, but differs in some of its Pi-binding characteristics. Similar to calcium carbonate, calcium acetate does not increase aluminium absorption.[60] Contrary to calcium carbonate, calcium acetate remains soluble at neutral pH and able to bind Pi across a wide pH range.[100,103] Therefore, impaired gastric acid secretion should not interfere with its Pi-binding capacity.[103] Calcium acetate can cause significant gastrointestinal adverse effects so that patient compliance may be worse than with calcium carbonate.[108,120] New formulations such as enteric-coated tablets result in improved tolerability without significant loss in Pi-binding capacity. They might also be associated with lower likelihood of hypercalcaemia.[121] Calcium acetate binds Pi more effectively than calcium carbonate.[13,106-109,113,120] Based on the calcium component, the acetate salt is about twice as effective as calcium carbonate in its Pi-binding capacity, allowing lower doses to be prescribed.[95,100,106,109,110] Despite lower doses, calcium acetate may still cause hypercalcaemia, especially when calcitriol is administered concomitantly.[95,110,113] Contrary to calcium carbonate-containing products which may contain lead, calcium acetate was found to be free of such contamination.[83]

4.5 Calcium α-Ketoglutarate

Calcium α-ketoglutarate is an analogue of glutamic acid, which was reported to bind phosphate efficiently.[122] Ketoglutarate is a central metabolite in the tricarboxylic acid cycle and a precursor of several nonessential amino acids.[123] Because of putative anabolic- and nitrogen-sparing effects, calcium α-ketoglutarate has been used to improve nutritional status of malnourished patients. In a study of patients receiving haemodialysis treatment, calcium α-ketoglutarate increased plasma arginine, proline and histidine concentrations, and reduced serum phosphorus concentrations.[124] Zimmermann et al.[125] administered calcium α-ketoglutarate at a dose of 4.5 g/day to 14 patients receiving haemodialysis treatment for 36 months. There was a reduction in serum phosphorus concentration from a mean of 8.0 ± 0.3 mg/dL (2.6 ± 0.1 mmol/L) at baseline to 5.9 ± 0.2 mg/dL (1.9 ± 0.07 mmol/L) following treatment with calcium α-ketoglutarate. Serum calcium concentration increased from baseline but remained within the normal range (mean 2.47 ± 0.08 mmol/L).

Bro et al.[126] compared the Pi-lowering capacity of calcium α-ketoglutarate with calcium carbonate in a randomised cross-over study of 19 patients receiving haemodialysis treatment. The mean plasma ionised calcium concentration was lower during calcium α-ketoglutarate treatment compared with calcium carbonate. After 12 weeks, there was no significant difference in plasma phosphorus concentration between calcium α-ketoglutarate and calcium carbonate treatments. However, the mean plasma phosphorus concentration decreased from 5.3 ± 0.2 mg/dL (1.7 ± 0.06 mmol/L) at baseline to 4.5 ± 0.3 mg/dL (1.45 ± 1.0 mmol/L) during calcium α-ketoglutarate treatment ($p = 0.03$).[126] The mean daily administered elemental calcium after 12 weeks of treatment was 2.44g (range 0.98–2.93g) for the calcium α-ketoglutarate and 2.6g (range 0.54–3.24g) for the calcium carbonate group. Five of 17 patients were withdrawn from the study because of gastrointestinal intolerance while on calcium α-ketoglutarate. All five patients had a history of gastrointestinal problems prior to the study.[126]

In another randomised, cross-over study of 28 patients receiving haemodialysis, calcium α-keto-

glutarate was compared with calcium acetate for the treatment of hyperphosphataemia.[123] The two drugs were used at doses that provided equimolar amounts of calcium to each patient. At 4 weeks, there was a significant reduction in serum phosphorus concentration from baseline in both groups (from 7.6 ± 1.9 to 6.0 ± 1.2 mg/dL [2.47 ± 0.63 to 1.95 ± 0.4 mmol/L] for calcium α-ketoglutarate; p = 0.0001 and from 3.37 ± 1.62 to 6.0 ± 1.8 mg/dL [2.40 ± 0.53 to 1.95 ± 0.6 mmol/L] for calcium acetate; p = 0.004). The incidence of hypercalcaemia (serum calcium >11.2 mg/dL) [>2.8 mmol/L] was much higher with calcium acetate than with calcium α-ketoglutarate (p = 0.03). Contrary to the previous study, calcium α-ketoglutarate was well tolerated by all patients and none discontinued the treatment.[123]

Based on the available information, calcium α-ketoglutarate appears to be a more potent Pi binder than calcium acetate, which itself is about twice as potent as calcium carbonate. Since lower amounts of elemental calcium are required to achieve the same degree of Pi-binding, calcium α-ketoglutarate is associated with a lower incidence of hypercalcaemia than other calcium salts.[123] Calcium α-ketoglutarate has been used as a Pi binder in Europe but not in the US. Although costing about 10 times more than calcium carbonate, its price is in the same range as calcium acetate. The beneficial metabolic effects of this compound justify its further development for use as a Pi binder in ESRD patients.

4.6 Adverse Effects of Calcium-Based Pi Binders

4.6.1 Hypercalcaemia

Due to absorption of calcium across the gastrointestinal mucosa, hypercalcaemia is a frequent adverse effect of calcium salts. Despite differences in solubility at different pH ranges, the percentage of calcium absorbed is roughly equal for calcium acetate, calcium carbonate and calcium citrate, amounting to about 30–32%.[100] Due to differences in Pi-binding capacity, lower doses of calcium acetate and calcium α-ketoglutarate are required to control hyperphosphataemia. The likelihood of hypercalcaemia with calcium-based Pi binders in descending order is: calcium citrate >calcium carbonate >calcium acetate >calcium α-ketoglutarate.

4.6.2 Adynamic Bone Disease

The increased use of calcium-containing Pi binders may have contributed to the increased incidence of adynamic bone disease and vascular calcifications in ESRD patients. In a study of 259 haemodialysis patients, adynamic bone disease was observed in half of the patients in whom a bone biopsy was available.[127] Aluminium intoxication, another cause of adynamic bone disease, was present in only one-third of the patients. In ESRD patients, serum PTH concentrations are maintained at approximately two to three times the upper limit of normal to overcome the skeletal resistance to PTH action.[22] PTH resistance is in large part due to hyperphosphataemia.[128] Therefore, better control of serum phosphorus concentrations may lead to a revision of these recommendations. Over-suppression of PTH production secondary to chronic hypercalcaemia and high dialysate calcium concentrations appear to be major contributing factors to adynamic bone disease.[127,129]

4.6.3 Soft Tissue and Vascular Calcification

Soft tissue and visceral calcifications have been reported both in adults and in children with ESRD and are associated with significant morbidity and mortality.[130-132] In a postmortem study of 120 children and adolescents, a strong association was found between calcitriol administration and soft tissue calcifications.[131] This study failed to show an association between serum phosphorus concentrations or Ca × P product and soft tissue calcification. In their analysis, the investigators used peak serum phosphorus concentration or phosphorus concentration at the time of death. It is possible that the average Pi concentrations over time are more relevant than phosphorus concentrations measured at a single point in time. Subsequent, larger studies have shown a clear association between high serum phosphorus concentrations and vascular calcifications or mortality, primarily from cardiac causes.[7,133-135] The chronic use of calcium-containing Pi binders is associated with a higher incidence of hypercalcaemia and coronary artery calcifications, when compared with calcium-free Pi binders.[136]

When treating hyperphosphataemia, the goal is to maintain Ca × P product below a level that might result in soft-tissue calcification. The critical threshold for Ca × P product was thought to be 60 or even 70 mg^2/dL^2 (4.8–5.6 $mmol^2/L^2$).[22,132] In view of recent epidemiological observations showing an association between high serum phosphorus or Ca × P product and excess mortality in patients receiving haemodialysis treatment,[7,135] the threshold of Ca × P product has been lowered and should be maintained below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$).[137] Assuming a serum calcium concentration of 10 mg/dL (2.5 mmol/L), the serum phosphorus must be kept below 5.5 mg/dL (1.77 mmol/L). The validity of these recommendations would require long-term outcome research.

5. Aluminium- and Calcium-Free Pi Binders

5.1 Sevelamer

Sustained increases in serum phosphorus concentrations and in Ca × P product have been shown to be associated with increased incidence of vascular calcifications[133] and increased mortality[7] in ESRD patients. The development of an aluminium- and calcium-free Pi binder, therefore, became an important goal.

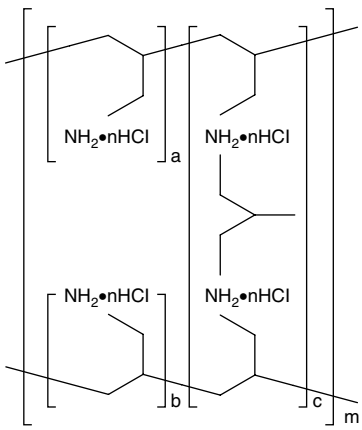

Fig. 2. Chemical structure of sevelamer (cross-linked poly(allylamine hydrochloride) [reproduced from Slatopolsky et al.,[144] with permission of Blackwell Scientific]). **a, b** = number of primary amine groups: **a + b** = 9; **c** = number of crosslinking groups: **c** = 1; **n** = fraction of protonated amines: **n** = 0.4; **m** = indicates extended polymer network.

Sevelamer is the only aluminium- and calcium-free Pi binder approved for control of hyperphosphataemia in patients with ESRD.[138] Sevelamer is a cationic polymer [poly(allylamine hydrochloride)], which binds phosphate anion by ion exchange and hydrogen bonding (figure 2). Sevelamer binds approximately 2.5–2.7 mmol Pi/g (table II). Maximum binding occurs between pH 6 and 8.[139] It is not absorbed by the gastrointestinal tract and is excreted in the faeces.[140] Sevelamer also binds and sequesters bile acids,[141] a property that may account for its ability to lower serum cholesterol concentrations.[141] When exposed to gastric and intestinal fluids, the gel undergoes hydration and swells to about 6–8 times its weight.[142] Since sevelamer binds Pi most effectively at neutral pH, changes in gastric acidity should not alter its effectiveness.[142] Initial preclinical studies in rats receiving sevelamer mixed with their diet, showed a dose-dependent reduction in urinary Pi excretion, indicating binding of dietary phosphorus by the gel.[142] In a nephrotoxic model of chronic renal insufficiency, 3% sevelamer mixed with the diet for 84 days, reduced serum phosphorus, arrested parathyroid hyperplasia and prevented the development of secondary hyperparathyroidism.[143]

The ability of sevelamer to inhibit Pi absorption in humans was shown in a study of 24 healthy volunteers receiving the drug for 18 days.[158] At the two highest doses (2.5 and 5.0g three times a day), sevelamer resulted in a significant increase in faecal Pi excretion and lower urinary Pi excretion compared with placebo.[158] There was also a significant reduction in serum cholesterol concentrations in the sevelamer-treated group. Serum phosphorus concentrations were not reported in this study.

In a randomised, placebo-controlled clinical trial in 36 patients receiving haemodialysis treatment, sevelamer administered for 2 weeks resulted in a significant reduction of serum phosphorus concentrations compared with placebo.[159] Serum phosphorus decreased by 1.2 mg/dL (0.38 mmol/L) in the sevelamer group and increased by 0.2 mg/dL (0.06 mmol/L) in the placebo group ($p = 0.037$).

In an open-label, dose-titration study of 48 patients receiving haemodialysis treatment, sevelamer

Table II. Major properties of new phosphate binders

Name	Class/specific properties	Pi-binding capacity (*in vitro* or *in vivo*)	Other characteristics	References
Calcium carbonate	Binder: binds Pi by physico-chemical reaction	4.65–17mg Pi/g compound (0.15–0.54 mmol/g)	Can cause hypercalcaemia, inexpensive	100,106,145
Calcium acetate	Binder: binds Pi by physico-chemical reaction	46.76–27mg Pi/g compound (0.218–0.87 mmol/g)	Can cause hypercalcaemia, moderately expensive	100,106,145
Sevelamer	Binder: polymer binds Pi by ion exchange and hydrogen bonding	l77.5–84mg Pi/g compound (2.5–2.7 mmol/g)	Aluminium- and calcium-free, can lower LDL-C and total cholesterol, very expensive	139,141,142
Lanthanum carbonate	Binder: binds Pi by physico-chemical reaction	N/A	Aluminium- and calcium-free, small amounts of lanthanum can be absorbed, high concentrations of lanthanum chloride can cause neurodevelopmental defects in young animals	146,147
Niceritrol	Possible inhibition of Pi transport due to formation of nicotinamide and NAD	N/A	Lipid-lowering properties, antiplatelet effects	53,55
Ferric ammonium citrate	Binder: binds Pi by physico-chemical reaction	17.7mg Pi/g compound (0.57 mmol/g)	No human data	148
Ferric citrate	Binder: binds Pi by physico-chemical reaction	19.8mg Pi/g compound (0.64 mmol/g)	Less effective than calcium carbonate in haemodialysis patients	148
Ferric chloride	Binder: binds Pi by physico-chemical reaction	36.9mg Pi/g compound (1.19 mmol/g)	No human data	148
Ferrihydrite	Binder: binds Pi by ligand exchange with hydroxide groups	11.8mg Pi/g compound (0.38 mmol/g)	Less effective than calcium carbonate, no human data	149,150
Mixed metal magnesium and iron hydroxyl-carbonate compounds	Binder: binds Pi by physico-chemical reaction	74.4–111.6mg Pi/g compound (2.4–3.6 mmol/g)	Less magnesium release than magnesium hydroxide, no human data	151,152
Cross-linked iron dextran	Binder: binds Pi by physico-chemical reaction	20–25mg Pi/g (0.65–0.81 mmol/g)	No human data, binding capacity low at pH 7 and highest at pH 2–3	153
Polynuclear iron hydroxide	Binder: binds Pi by physico-chemical reaction	41.2mg Pi/g compound (1.33 mmol/g)	Pi binding stable between pH 3-8	154,155
Cross-linked iron (III) chitosan	Binder: binds Pi by physico-chemical reaction	16.7–23.6mg Pi/g compound (0.54–0.76 mmol/g)	Can lower serum cholesterol, no published human data on the use of this compound as Pi binder	145,156,157

LDL-C = low density lipoprotein-cholesterol; **N/A** = not available; **NAD** = nicotinamide adenine dinucleotide; **Pi** = phosphate.

was administered for 8 weeks. The dose was increased every 2 weeks to achieve the desired serum phosphorus concentration.[160] Serum phosphorus reached the nadir of 6.5 mg/dL (2.1 mmol/L) after 7 weeks of treatment. Serum PTH concentrations declined from a mean of 395 to 283 ng/L. There was also a decline in serum total and low density lipoprotein-cholesterol (LDL-C) concentrations.[160] In another open-label study involving 15 patients receiving haemodialysis treatment, sevelamer was administered during 8 weeks with the dose titrated at 2-week intervals to maintain serum phosphorus concentrations below 5.5 mg/dL (1.77 mmol/L).[161] This study also showed that sevelamer can lower serum phosphorus concentrations and result in a reduction of serum PTH concentrations. The beneficial effects of sevelamer on the lipid profile were also confirmed.

Slatopolsky et al.[144] studied the short-term safety and efficacy of sevelamer in a multicentre, open-label, dose-titration study of 172 patients receiving haemodialysis treatment. After a 2-week washout

period, the patients with serum phosphorus >6.0 mg/dL (>1.94 mmol/L) were included in the study, and received three different doses of sevelamer for 8 weeks with dose titration every 2 weeks. Mean serum phosphorus concentration declined from a post-washout concentration of 9.1 ± 1.9 mg/dL (2.94 ± 0.77 mmol/L) to 6.6 ± 1.9 mg/dL (2.1 ± 0.6 mmol/L) after 8 weeks ($p < 0.0001$). Median serum PTH concentration declined from 316 ng/L at the end of the washout period to 224 ng/L at the end of 8-week treatment ($p < 0.0001$).[144] Despite a significant decline, serum phosphorus concentrations remained relatively high in this study.

Chertow et al. treated 192 patients receiving haemodialysis treatment with sevelamer for 44 weeks.[162] The dose of sevelamer was titrated monthly. The analysis was based on three prespecified sevelamer doses: low (<5.0g), medium (5.0–6.75g) and high (>6.75g). There was a sustained reduction in serum phosphorus concentration for the duration of the study. By the end of the treatment, the mean change in serum phosphorus from baseline was –2.2 ± 2.4 mg/dL (–0.71 ± 0.77 mmol/L) and the mean change in Ca × P product was –18.1 ± 22.0 mg^2/dL^2 (–1.46 ± 1.78 $mmol^2/L^2$) [$p < 0.0001$].[162]

Several studies have been conducted to assess the effect of sevelamer on the incidence of hypercalcaemia, Ca × P product and serum PTH concentrations.

In a study of 19 patients receiving haemodialysis treatment, sevelamer, administered for 6 weeks, resulted in a significant reduction in Ca × P product (from 64.1 ± 14.1 to 46.9 ± 7.4 mg^2/dL^2 [5.13 ± 1.13 to 3.75 ± 0.59 $mmol^2/L^2$]), which was due to declines in both serum phosphorus and calcium concentrations.[163] In an open label cross-over study of 84 patients receiving haemodialysis treatment, sevelamer was compared with calcium acetate in its ability to lower serum phosphorus concentrations.[164] After 8 weeks of stable treatment, the mean change in serum phosphorus concentration from baseline was comparable between the two treatments, i.e. –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. Hypercalcaemic episodes, defined as at least one serum calcium concentration >11.0 mg/dL (>2.75 mmol/L), were significantly lower with sevelamer than calcium acetate (5% vs 22% for sevelamer and calcium acetate, respectively).

Chertow et al.[165] conducted a randomised clinical trial in 200 patients receiving haemodialysis treatment, comparing sevelamer with a calcium-based Pi binder administered for 52 weeks. The dose of Pi binder was titrated every 3 weeks to achieve serum phosphorus and calcium concentrations in the target range. Calcification scores for coronary arteries and for the aorta were determined by electron beam tomography. Serum phosphorus concentrations were equally controlled with the two treatments but serum calcium concentrations were higher in the calcium binder-treated group (9.5 ± 0.6 versus 9.7 ± 0.7 mg/dL [2.37 ± 0.15 versus 2.42 ± 0.17 mmol/L] for sevelamer and the calcium binder-treated group, respectively; $p = 0.002$). The incidence of hypercalcaemia was 17% in sevelamer-treated patients compared with 43% in calcium binder-treated patients.[165] 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).[138,165] These findings have been replicated and recently reported in another study.[166]

In a recent case-control study of patients receiving haemodialysis treatment, mortality was compared between those receiving sevelamer and those receiving either calcium carbonate or calcium acetate for 1 year.[167] There was a reduction in cardiac causes of mortality in the sevelamer-treated group compared with the calcium carbonate-treated group but not the calcium acetate-treated group. The sevelamer-treated patients were younger and included a higher percentage of women and more patients receiving peritoneal dialysis. These factors might be responsible, in part, for the reduced mortality in sevelamer-treated patients.

An additional therapeutic effect of sevelamer is its ability to bind and sequester bile acids[141] resulting in a favourable lipid profile. In a dose-titration study of 12 haemodialysis patients receiving sevelamer for 8 weeks, there was 23% fall in total cholesterol and 35.9% fall in LDL-C. High density lipoprotein-cholesterol (HDL-C) and fat-soluble vi-

tamins were not affected.[161] In a longer-term study of 46 weeks' duration, sevelamer reduced LDL-C by 30% and increased HDL-C by 18% from baseline.[162] Because increased LDL-C and reduced HDL-C are commonly observed in patients with CRF,[168] this additional effect may be advantageous in such patients. Sevelamer might therefore have the ability to reduce cardiovascular complications by two independent mechanisms: reduction of the formation of atherosclerotic plaques and prevention of Pi-induced vascular calcifications.[165]

Sevelamer is generally well tolerated with adverse events similar to placebo or to calcium acetate.[169] The adverse events that may be possibly related to the drug are nausea (7%), constipation (2%), diarrhoea (4%) and dyspepsia (5%).[169] Since sevelamer does not provide any base similar to calcium carbonate or acetate, a potential problem with the use of sevelamer would be the development or worsening of metabolic acidosis.[170] Transient declines in serum bicarbonate concentrations were reported in a study of 16 stable haemodialysis patients receiving a relatively low dose of sevelamer (2.0 g/day).[171] This problem is more likely to occur at higher doses or in pre-dialysis patients, since dialysis can partially correct the acidosis. A problem that is shared with other Pi binders is the necessity to 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 6.3g, which translates to 16 capsules a day.[162] The recent introduction of 800mg tablets may partially solve this problem. A major disadvantage for sevelamer compared with calcium-containing Pi binders is its high cost. The average monthly cost of sevelamer is $US108.98 (2002 value) compared with $US26.76 for calcium acetate (PhosLo®[1] and $US5.22–$US8.06 for calcium carbonate.[172] Other reports have estimated the yearly cost of treatment with sevelamer to be $US2500 (2003 value), compared with $US190–$US320 for calcium acetate and $US40 for calcium carbonate.[173]

To reduce costs, it has been suggested to combine sevelamer with a calcium-containing Pi binder, each used at a lower dose than would be required if used as monotherapy. In addition to lower cost, the calcium-based binder would provide a source of base to treat acidosis while also reducing the risk of rising PTH concentrations. McIntyre et al.[174] studied the effect of combination calcium-based Pi binder and sevelamer for 8 weeks in 23 patients with mild hypercalcaemia undergoing haemodialysis treatment. Serum calcium fell from a mean of 11.2 ± 0.16 to 10.24 ± 0.12 mg/dL (2.8 ± 0.04 to 2.56 ± 0.03 mmol/L) [$p < 0.0005$]. The percentage of patients with hypercalcaemia fell markedly from 100% to 26%. There was no significant change in serum phosphorus concentration. PTH concentrations increased from 166 ± 47 to 276 ± 104 ng/L ($p = 0.02$). The average daily dose of sevelamer was 2.77 ± 0.36g (range 0–5.6g), which is significantly lower than 4.9 g/day, the dose required in another study when sevelamer was used alone.[164] In a study of 71 patients receiving haemodialysis treatment, the provision of 900mg elemental calcium each night in conjunction with sevelamer treatment resulted in better control of hyperparathyroidism without a significant change in serum calcium concentrations.[175] Preliminary evidence suggests that the incidence of adynamic bone disease might be lower with combination therapy compared with calcium-based binders used alone.[176]

In summary, sevelamer is an aluminium- and calcium-free Pi binder based on a novel chemical structure. It is not absorbed and shows a high Pi binding capacity. Its efficacy and safety have been demonstrated in several well-conducted clinical studies. Sevelamer is as effective as calcium carbonate or calcium acetate with significantly lower incidence of hypercalcaemia, while maintaining the ability to suppress PTH production. An additional benefit of sevelamer is its ability to lower LDL-C and total cholesterol 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, the necessity to take large doses and the possibility of induction of metabolic acidosis. Overall, sevelamer offers many advantages over the existing Pi binders.

In addition to sevelamer, which has been approved for treatment of hyperphosphataemia in pa-

1 Use of the registered name is for identification purposes only and does not imply endorsement.

tients with ESRD, several other aluminium- and calcium-free compounds are being developed as potential Pi binders. The available preclinical data on these compounds are summarised in table II and discussed in more detail in the next several sections.

5.2 Rare Earth Metals

5.2.1 Lanthanum and Zirconium Chloride

Salts of two rare earth metals have been evaluated in preclinical studies for their ability to bind Pi and lower serum phosphorus concentrations. Lanthanum chloride hydrate, administered to rats with normal renal function, was found to be as effective as aluminium chloride hexahydrate in reducing intestinal Pi absorption during a 21-day study period.[177] In longer studies (100 days), the drug was found to accumulate in several tissues with highest concentrations found in the liver.[177] Another drug, zirconyl chloride octahydrate, was evaluated in a similar fashion. In a 21-day study in rats, zirconyl chloride was found to be as effective as aluminium chloride hexahydrate in reducing intestinal Pi absorption.[178] Contrary to the lanthanum salt, the zirconium salt did not accumulate in tissues. No further studies have been reported for this compound.

Lanthanides have been shown to block calcium channels in human and animal cells.[179] They can affect the action of enzymes such as Ca^{2+}-adenosine triphosphatase (ATPase) and magnesium (Mg^{2+})-ATPase in many tissues including neurons.[180] In a rat pulmonary macrophage primary culture system, lanthanum chloride showed evidence of cytotoxicity (median lethal concentration [LC_{50}] = 52 μmol/L) with regard to several parameters studied.[146] Neurodevelopmental defects have been observed in newborn mice exposed to lanthanum chloride during conception and 30 days postnatally.[181] These studies point to potentially serious toxicity with chronic use of lanthanum chloride. It is not known whether other lanthanum salts such as lanthanum carbonate are toxic. Therefore, evaluation of long-term toxicities will be necessary prior to approval of these compounds for use in humans.

5.2.2 Lanthanum Carbonate

The carbonate salt of lanthanum has shown significant promise as a Pi binder for use in humans. The phase II and III trials have been completed and the drug is currently under consideration for approval as a Pi binder both in the US and in Europe.

Lanthanum carbonate was evaluated in a placebo-controlled, dose-titration study in 145 patients receiving haemodialysis treatment.[182] The patients received doses ranging from 225 to 2250 mg/day of the drug for up to 6 weeks. There was a dose-dependent decrease in serum phosphorus concentrations which was statistically significant ($p < 0.05$) for doses of 1350 and 2250 mg/day. Serum lanthanum concentrations at the end of the study were 0.10 ± 0.23 μg/L (0.22 ± 0.5 nmol/L) for placebo and ranged from 0.23 ± 0.23 to 1.16 ± 1.91 μg/L (0.5 ± 0.5 to 2.53 ± 4.16 nmol/L) for the lowest to the highest dose of lanthanum carbonate.[147]

Lanthanum carbonate was used in 126 patients receiving haemodialysis treatment in a randomised, placebo-controlled, parallel group study. After a 3-week washout, the patients entered a 6-week dose-titration phase, followed by a 4-week maintenance phase.[183] Lanthanum dose varied from 1500–3000 mg/day. Hyperphosphataemia, defined as a serum phosphorus concentration >5.9 mg/dL (>1.9 mmol/L), was controlled in 59% of lanthanum-treated patients versus 23% of patients on placebo.[183] The mean serum phosphorus concentration was significantly lower in the lanthanum-treated patients compared with the placebo-treated group ($p < 0.0001$). There was a reduction in Ca × P product in the lanthanum-treated group compared with the placebo group ($p < 0.0001$). The drug was generally well tolerated with adverse events occurring at higher doses.[184] The most common adverse events were nausea and vomiting, each occurring in 6% of lanthanum-treated patients versus 2.3% and 4.5% of placebo-treated patients. Serum lanthanum concentrations increased from baseline but remained extremely low (maximum 0.776 μg/L [1.6 nmol/L]).

Previous studies in rats with CRF had indicated that lanthanum carbonate might affect bone formation.[185] These initial concerns were lifted in subsequent studies. A recent study evaluated bone changes in patients receiving lanthanum carbonate or calcium carbonate for 1 year. Lanthanum resulted in improvements in the majority of bone biopsy parameters studied. Adynamic bone disease was present in 17% of calcium carbonate-treated patients

but in none of the lanthanum-treated patients. Bone lanthanum concentrations remained below 6 μg/g wet weight.[176]

The preliminary results of phase III trials of lanthanum carbonate have been published in abstract form.[176,183-187] In a randomised, open-label, controlled trial, lanthanum carbonate was compared with calcium carbonate in 800 ESRD patients (533 on lanthanum carbonate and 267 on calcium carbonate). The median daily dose required for phosphate control was 2250mg for lanthanum carbonate and 3000mg for calcium carbonate.[187] Lanthanum carbonate treatment resulted in lower Ca × P product. Clinically significant hypercalcaemia was observed in 20.2% of patients receiving calcium carbonate and in 0.4% of patients receiving lanthanum carbonate. In another long-term study,[186] lanthanum carbonate was administered to haemodialysis patients. The interim analysis included 616 patients receiving lanthanum carbonate and 612 patients receiving standard therapy with 98 patients having completed 2 years of treatment. Serum phosphorus was controlled equally well with lanthanum carbonate and with conventional Pi binders (aluminium salts, calcium salts, sevelamer). There were twice as many deaths in the conventional treatment group as in the lanthanum carbonate group. Because of the preliminary nature of these results, one should await the completion of the study to fully evaluate the safety of lanthanum carbonate and its possible beneficial effect on mortality in this patient population.

Several new compounds based on modified lanthanum carbonate are in early stages of development. Two compounds (Renazorb™ B and H) are reported to be more insoluble than unmodified lanthanum carbonate, which could potentially reduce lanthanum absorption by the gastrointestinal tract. 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.

In summary, lanthanum carbonate is a new Pi binder which has been shown to be as effective as calcium carbonate with significantly lower incidence of hypercalcaemia. Lanthanum carbonate is well tolerated and is likely to become the second aluminium- and calcium-free Pi binder for the treatment of Pi retention in ESRD. Its therapeutic effect is limited to the control of Pi absorption with no effect on serum lipids. The systemic absorption of lanthanum carbonate appears to be low with serum lanthanum concentrations ≥1000-fold lower than those associated with *in vitro* cytotoxicity. Long-term safety follow-up would be necessary to determine if chronic low level exposure to lanthanum carbonate could result in any serious adverse health consequences.

5.3 Magnesium Salts

Magnesium salts can bind Pi and may be considered an alternative to calcium salts. However, significant amounts of magnesium can be absorbed by the intestine with the potential risk of accumulation and toxicity in patients with renal failure.[188] Several studies on the use of magnesium salts as Pi binders have been reported. Many involve small numbers of patients, inadequate controls and other flaws in experimental design. Magnesium hydroxide (≤3 g/day) was used for ≤12 weeks in nine patients undergoing haemodialysis.[189] The dialysate magnesium level was not reduced. Despite a very high pretreatment serum phosphorus concentration of 9.0 mg/dL (2.9 mmol/L), serum phosphorus decreased only 0.9 mg/dL (0.29 mmol/L). In another study, magnesium hydroxide was used in 18 patients receiving haemodialysis treatment who were switched to a magnesium-free dialysate.[190] Serum phosphorus concentrations increased during magnesium-only treatment but decreased when aluminium hydroxide was added. Surprisingly, PTH concentrations fell despite lack of phosphorus control. In a long-term study, magnesium hydroxide (average dose 2.6 ± 2.0 g/day) was administered for 6–20 months to 32 patients receiving haemodialysis treatment.[191] Dialysate magnesium was reduced to 0.91 mg/dL (0.375 mmol/L) and the dose was adjusted to prevent hypermagnesaemia. Serum phosphorus concentrations decreased from 5.4 ± 1.2 to 5.1 ± 0.9 mg/dL (from 1.76 ± 0.4 to 1.66 ± 0.3 mmol/L). Despite the use of a low magnesium dialysate, serum magnesium concentration increased from 2.18 ± 0.45 to 3.5 ± 0.45 mg/dL (from 0.96 ± 0.2 to 1.54 ± 0.2 mmol/L). Many patients developed hyperkalaemia and diarrhoea.[191] Based on these studies magnesium

hydroxide salt does not appear to be an effective or safe Pi binder.

In a long-term study at a single centre, magnesium carbonate was used as a Pi binder for 2 years in 28 patients receiving haemodialysis treatment.[192] The dialysate bath was changed to a magnesium-free dialysate. Serum phosphorus and PTH concentrations remained unchanged while on magnesium carbonate. Only mild and transient diarrhoea was observed.

Delmez et al.[193] performed a randomised, controlled, cross-over study of 29 patients receiving haemodialysis treatment who received either calcium carbonate or a combination of calcium carbonate at half the previous dose plus magnesium carbonate. Patients were dialysed with a dialysate bath containing 0.6 mg/dL (0.247 mmol/L) magnesium. After a 4-week washout, the treatment allocations were reversed. The doses were titrated weekly to attain the desired phosphorus concentration. At the completion of the first phase and prior to the washout, patients also received increasing doses of intravenous calcitriol for 4 weeks. The mean phosphorus concentration was 5.7 ± 0.2 mg/dL (1.84 ± 0.06 mmol/L) with the magnesium carbonate plus calcium carbonate combination and 5.2 ± 0.2 mg/dL (1.68 ± 0.06 mmol/L) when calcium carbonate was used alone. Serum magnesium concentrations were not different between the two groups and averaged 3.0 mg/dL (1.23 mmol/L). The amount of elemental calcium used was lower during the combined magnesium carbonate and calcium carbonate phase compared with the calcium carbonate monotherapy phase of the study (1.2 ± 0.29 versus 2.9 ± 0.4 g/day, $p < 0.0001$), despite the ability to use higher doses of calcitriol. These studies show that magnesium carbonate is better tolerated than magnesium hydroxide and, under controlled conditions, could be used as a Pi binder in patients with hypercalcaemia.

A fixed-dose combination of magnesium carbonate and calcium carbonate (MagneBind™) has been promoted by the manufacturer as a Pi binder. Because this combination is marketed as a nutritional supplement it is not subject to rigourous clinical trials and US Food and Drug Administration approval for this indication. However, based on the literature reviewed above, magnesium carbonate could be considered as an alternative Pi binder, especially when combined with low dose calcium carbonate. Since magnesium can accumulate in patients with renal failure, the use of magnesium-containing compounds is restricted to patients who are on chronic haemodialysis. The use of low magnesium dialysate (0.247 mmol/L [0.6 mg/dL]) has been shown to be well tolerated and not associated with muscle cramping seen with magnesium-free dialysate.[193] Mild hypermagnesaemia in the range of 3 mg/dL (0.123 mmol/L) may not be harmful and may even have some beneficial effects. Elevated serum magnesium concentrations are associated with a reduced incidence of arterial or mitral valve calcifications,[194,195] suggesting that magnesium may protect against the development of soft tissue calcifications, independent of serum calcium or phosphorus concentrations.[195]

5.4 Iron-Based Compounds

It had been observed for several decades that iron administration can result in a reduction in serum phosphorus concentrations, Pi depletion or rickets in various animal models.[196-198] Hypophosphataemia has also been observed after intravenous iron administration but in this instance, hypophosphataemia may be caused by multiple factors.[154,199] These early findings were not pursued until recently, when the need for an aluminium- and calcium-free Pi binder became obvious. This led to additional experiments to explore the possible use of iron-containing compounds as Pi binders.[154]

Cross-linked iron dextran was studied as a possible Pi binder. *In vitro* studies show that it has relatively low affinity for Pi. Maximum binding capacity is achieved at pH 2–3 and is 30% lower at neutral pH[153,200] (table II). When administered orally to rats for 4 weeks, iron dextran was well tolerated and able to bind Pi without iron release.[153] Serum phosphorus concentrations remained unchanged but there was a 15-fold reduction in urinary Pi excretion, suggesting reduced intestinal Pi absorption.[153] There was no evidence of toxicity after 8 weeks of exposure. Although not addressed in this study, allergic reactions seen with intravenous iron dextran should not occur with oral use. It remains to be seen if iron dextran will be able to reduce intestinal Pi absorption and lower serum phosphorus concentrations in humans.

Polynuclear iron hydroxide was shown to bind phosphate *in vitro* and form insoluble iron-phosphate complexes.[155] The binding of Pi to this compound is relatively stable between pH 3 and 8. In studies conducted in white mice, approximately 0.5% of the iron was absorbed. In humans, 1g of polynuclear iron hydroxide binds approximately 41.3mg (1.33 mmol) of Pi (table II). Based on these encouraging preclinical data, Hergesell and Ritz[154,155] studied the effect of stabilised polynuclear iron hydroxide in an open-label, uncontrolled study of 13 patients with chronic renal insufficiency (median serum creatinine 5.4 mg/dL [477 mmol/L]). After a 2-week washout period, patients received 7.5g of stabilised polynuclear iron hydroxide with meals for 4 weeks. There was a 20% decrease in median plasma phosphorus concentration (from 6.8 to 5.3 mg/dL) [2.2 to 1.7 mmol/L] and 37% reduction in median urinary Pi excretion (from 837 to 503 mg/day) [from 27.0 to 16.3 mmol/day]. However, these values remained elevated in many patients. There were no significant changes in serum iron or serum ferritin concentrations. Except for increased number and black discolouration of stools, there were no other notable adverse effects.[155]

The non-ionic ferric polymaltose complex was studied in 32 uraemic patients receiving haemodialysis treatment with hyperphosphataemia (serum phosphorus >5.5 mg/dL) [>1.78 mmol/L].[201] The study was an open-label, cross-over study with 2-week washout and 8-week treatment periods. The study patients received ferric polymaltose complex (596mg [10.68 mmol] iron per day), while the control group was continued on their previous Pi binders, either aluminium hydroxide or calcium carbonate. After another washout, the treatment allocation was reversed.[201] Mean serum phosphorus concentration after the washout period was 8.0 ± 1.5 and 7.8 ± 1.4 mg/dL (2.61 ± 0.50 and 2.52 ± 0.46 mmol/L) for the iron-treated and the control groups, respectively. Mean phosphorus concentrations decreased steadily during the study, reaching 7.0 mg/dL (2.26 mmol/L) in the iron group and 5.2 mg/dL (1.68 mmol/L) in the control group. The mean serum phosphorus concentrations were lower at the end of the second washout period, decreasing on average 0.77 mg/dL (0.25 mmol/L) for the iron and 2.3 mg/dL (0.75 mmol/L) for the control group ($p < 0.001$). Adverse effects were minimal with three patients reporting loose stools.[201] This study, therefore, showed that ferric polymaltose complex is somewhat less effective than calcium-based Pi binders in lowering serum phosphorus concentrations in patients receiving haemodialysis treatment.

Another iron salt studied as a possible Pi binder is synthetic ferrihydrite.[149] It specifically adsorbs Pi by ligand exchange with hydroxyl groups on its surface[149] (table II). In an acute study (3 hours), the effect of ferrihydrite on intestinal Pi absorption was determined in 30 rats (five per group) receiving no drug (controls), two different doses of calcium acetate or three different doses of ferrihydrite, administered by gavage. Both calcium acetate and ferrihydrite resulted in a dose-dependent reduction of Pi absorption. Based on the weight of the compounds, calcium acetate was twice as effective as ferrihydrite in suppressing Pi absorption. *In vitro* studies have shown binding capacity of approximately 11.8mg Pi/g ferrihydrite (0.38 mmol/g),[150] similar to that reported for calcium acetate.[100] It is not clear if iron can be absorbed from ferrihydrite since iron absorption was not measured in this study. These results are promising and should be confirmed in studies of longer duration.

Iron (III)-saccharide complex is acid resistant with a higher capacity to bind Pi than iron (III) hydroxide.[202] It was administered to normal rats to assess its ability to bind phosphate *in vivo*.[202] The animals received 1–8% iron (III)-sucrose complex by gavage for 7 days. Phosphate balance studies were performed to determine the amount of Pi in the faeces and urine. Faecal Pi was reduced in rats receiving doses of 2% or higher. This was associated with a drop in urinary Pi excretion. Serum phosphorus concentrations were not reported in this study. Similar to the previous study, the results are encouraging and require further confirmation in long-term animal and human experiments.

Hsu et al.[148] tested several ferric compounds for their ability to bind Pi in both normal and azotaemic (partially nephrectomised) rats. These included ferric ammonium citrate, ferric citrate and ferric chloride, administered for a period of 4 weeks. All three ferric compounds reduced intestinal Pi absorption, as determined by higher faecal Pi excretion. Pi-binding capacity ranged from 17.7 to 37mg Pi/g

compound (0.57 to 1.19 mmol/g), being lowest with ferric citrate and highest with ferric chloride (table II). Plasma iron concentration was higher in iron-treated groups compared with controls and reached the significance level in the ferric citrate-treated animals. Although ferric chloride showed the highest capacity to bind Pi, it resulted in stunted growth and reduced creatinine excretion in the study animals.

Ferric citrate was studied as a possible Pi binder in 54 patients receiving haemodialysis treatment in an open-label, cross-over trial.[203] Following a 2-week washout, the patients were randomly assigned to receive either ferric citrate or calcium carbonate (3g of each binder). After 4 weeks of treatment and a second washout, the patients were crossed over to the other agent.[203] At the completion of the study, there was a significant reduction of serum phosphorus concentration with both calcium carbonate and ferric citrate (from 7.2 ± 1.9–5.2 ± 1.5 mg/dL [2.32 ± 0.61–1.68 ± 0.48 mmol/L] for calcium carbonate and 6.7 ± 1.9–5.7 ± 1.6 mg/dL [2.16 ± 0.61–1.84 ± 0.52 mmol/L] for ferric citrate). However, the absolute decrement in serum phosphorus was higher in calcium carbonate-treated patients. Adverse events with ferric citrate included black stools and gastrointestinal symptoms such as diarrhoea or constipation. Ferric citrate, therefore, appears to be slightly less effective than calcium carbonate but has the advantage of preventing calcium accumulation. Although serum aluminium concentrations were not increased in ferric citrate-treated patients, citrate salts are known to increase aluminium absorption and should not be administered with aluminium salts.

Burger et al.[156] studied cross-linked iron (III) chitosan for its ability to bind Pi *in vitro*. Maximum Pi-binding capacity of this compound was 23.6mg Pi/g compound (0.76 mmol/g). About 16% of iron was dissociated from the complex. *In vivo* studies were performed in 15 young rats receiving either ferric sulphate or cross-linked iron (III) chitosan. The number of animals in each group and the Pi composition of their diet were not specified. Furthermore, animals were placed on 1.2% Pi in water for 30 days, which was discontinued before starting the study drugs. Therefore, a decline in serum phosphorus could be, in part, due to discontinuation of Pi supplements. At the end of the study, there was a 32.7% decline in serum phosphorus in chitosan group and 37% in iron sulphate-treated group.[156] There was a slight increase in serum iron, suggesting iron release from both iron salts. This study was limited by its design and the results must be viewed with caution.

Baxter et al.[145] performed both *in vitro* and *in vivo* studies to demonstrate the ability of iron (III) chitosan to bind Pi and lower serum phosphorus concentrations. *In vitro* binding studies showed equal binding capacity for Pi at pH 2.0 and 7.4 (17 and 15.6 mg/g [0.54 and 0.50 mmol/g], respectively) [table II]. Iron (III) chitosan was also used in a randomised, double-blind, placebo-controlled study in rats (16 per group) receiving either a standard chow with 0.4% Pi and 1% fibre (controls) or the same diet plus 1% iron (III) chitosan. A group of six rats were used to determine baseline laboratory values. There was an increase in faecal Pi content associated with lower serum phosphorus concentration and lower Ca × P product in the treatment group when measured at 30 days. Serum phosphorus decreased from 5.5 ± 0.9 to 4.1 ± 0.6 mg/dL (from 1.77 ± 0.29 to 1.32 ± 0.19 mmol/L). Of concern is an unexplained increase in the kidney Pi content of the treated animals compared with controls. There was also an increase in serum iron concentration in treated animals compared with controls but iron concentration was similar to that of animals used for baseline. The investigators calculated that the amount of iron administered in this study was 28 times less than in similar studies with iron dextran[153] and 18 times less than with iron citrate.[148] These studies are proof of concept that iron-chitosan complexes are effective Pi binders with minimal release and absorption of iron. A potential additional benefit of chitosan is its ability to lower serum cholesterol.[157] If these findings are confirmed, iron (III) chitosan could be considered a worthwhile pharmacological agent for the treatment of hyperphosphataemia in patients with ESRD.

In summary, iron-based compounds are able to bind Pi and reduce its intestinal absorption. A small amount of iron may be released from these compounds and systemically absorbed. This is not necessarily undesirable. Patients on haemodialysis receive epoetin-alfa for the treatment of chronic renal

anaemia. These patients develop functional iron deficiency and iron supplementation becomes necessary to prevent depletion of iron stores as iron is incorporated into newly formed red blood cells.[204] Therefore, absorption of small amounts of iron could be beneficial and might help reduce the need for parenteral iron administration. Polynuclear iron hydroxide has high *in vitro* Pi-binding capacity but a short-term human study showed mild and variable reduction in serum phosphorus concentrations.[155] Iron (III) chitosan appears to be associated with less iron absorption and may have the added benefit of lowering serum cholesterol concentrations. Unfortunately, controlled studies in human patients have not been reported.

5.5 Mixed Metal Hydroxyl Carbonate Compounds

Rankin et al.[205] synthesised a series of compounds based on mixed metal hydroxide structures incorporating iron and calcium or iron and magnesium (code named CT). *In vitro* studies showed that these compounds are potent Pi binders with binding capacity being independent of pH.[151,205] Compared with standard Pi binders, Pi-binding capacity of the iron and magnesium-containing compound (CTFeMg) was higher than the iron- and calcium-containing compound CTFeCa or CT100 (a hydrotalcite), which in turn were more potent Pi binders than magnesium hydroxide and calcium carbonate, tested under identical conditions[205] (table II). These compounds were also tested *in vivo* in normal rats, using four animals per group. Following oral administration (1% mixed with food) for 1 week, urinary and faecal Pi excretion were measured during a 24-hour metabolic balance study.[152] Twenty-four-hour urinary Pi excretion was 0.4 ± 0.12mg (13 ± 4 μmol) for CTFeMg, 0.8 ± 0.34mg (26 ± 11 μmol) for CT100, 2 ± 1.6mg (65 ± 53 μmol) for magnesium hydroxide and 2.2 ± 1.37mg (72 ± 44 μmol) for CTFeCa, compared with 23.75 ± 5.82mg (766 ± 188 μmol) in control rats. Plasma iron did not increase in rats receiving CTFeCa compared with controls but plasma magnesium was higher in rats receiving CTFeMg.[152] Unfortunately, plasma phosphorus measurements were not reported in this study. Based on these findings, mixed metal hydroxyl-carbonates are effective Pi binders and deserve testing in humans.

6. Conclusion

After almost 2 decades with only one new molecular entity approved for the treatment of hyperphosphataemia, there has been a renewed interest in the development of new Pi binders. A better understanding of the risks associated with the use of calcium-containing Pi binders in ESRD patients, including increased cardiac and vascular calcifications and increased mortality, has provided the impetus to develop calcium-free Pi binders. The adverse effects associated with the use of aluminium-containing binders in ESRD patients have also mandated the development of aluminium-free Pi binders. The use of metal ions as Pi binders should be approached with caution since accumulation of some metals in patients with CRF could result in potentially serious adverse consequences. The emphasis should therefore be on the development of compounds in which the metal is tightly attached to a support, allowing it to bind Pi without being released and absorbed. Increasing Pi-binding capacity by attaching several Pi-binding units to a support would also help reduce the large doses currently required to control serum phosphorus concentrations. This would help increase patient compliance, which is typically low. Finally, a neglected area of research is the development of compounds that specifically inhibit the active carrier-mediated intestinal Pi transport without systemic absorption.

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