Cardiovascular and Renal

Emerging drugs for hyperphosphatemia

Guido Bellinghieri, Domenico Santoro † & Vincenzo Savica
University of Messina, Division of Nephrology and Dialysis, Policlinico Universitario,
Viale Gazzi – 98100, Messina, Italy

Cardiovascular mortality is the leading cause of death in the uremic patient. Hyperphosphatemia is considered an independent risk factor associated with cardiovascular morbidity and mortality in dialysis patients. As phosphate control is not efficient with diet or dialysis, phosphate binders are commonly prescribed in patients with chronic renal failure. Aluminum salts, the first phosphate binders, even if effective, have several side effects due to their deposition in CNS, bone and hematopoietic cells. Calcium-containing phosphate binders, used in the last 15 years, increase total body calcium load and may exacerbate metastatic calcification, thus, increasing the risk of cardiovascular mortality. Recently two new compounds non-aluminum and non-calcium phosphate binders, sevelamer hydrochloride and lanthanum carbonate, have been introduced. Sevelamer, besides the effect on phosphate, has been associated with reduction of coronary and aortic calcification and with other pleiotropic effects especially on lipid metabolism. Lanthanum carbonate has similar phosphate control to calcium-based binders with less incidence of hypercalcemia but long-term clinical studies are needed for testing long-term exposure. Recently the authors found in dialysis patients, that salivary phosphorus correlated with serum phosphorus. Therefore, they supposed that the use of salivary phosphate binders could reduce its absorption and represent a chance for reducing the serum phosphate concentration in uremic patients.

Keywords: dialysis, hyperphosphatemia, phosphate binder, vascular calcification

1. Background

Hyperphosphatemia is a well recognized complication, both in patients with chronic renal disease and in those in dialysis [1,2]. Frequent complications in uremic heart are characterized by calcification of coronary vessels, cardiac valves and myocardial tissue, as well as myocardial fibrosis, resulting in structural dysfunction. Depending on the age of the patient population examined, 54 – 100% (mean 83%) of dialysis patients in case series have some degree of coronary artery calcification. Coronary vascular calcification was also present in adolescents and young adults with chronic kidney disease (CKD) [3]. In the dialysis population, cardiovascular mortality is the leading cause of death, with mortality 10 – 30-times higher than in the general population, despite stratification for sex, race and presence of diabetes. The high cardiovascular mortality has been related with disturbances in mineral metabolism (increased levels of calcium and phosphate) and abnormal bone (osteodystrophy) [4,5]. The principal factor in the process of vascular calcification is hyperphosphatemia. Serum phosphorus concentrations > 5.0 mg/dl were associated with an increased relative risk of death. The adjusted mortality risk increased by 20 – 40% with rises in inorganic phosphate, > 4.2 mg/dl [5]. Investigators of the US Renal Data System showed a 27% increase in the relative risk (RR) of death associated with serum
Filtration rates decline < 40 ml/min/1.73 m², whereas in early renal failure (CRF), it becomes evident once the glomerular functionally severe in ARF secondary to rhabdomyolysis. In chronic disease (ESRD), for a defect in urinary phosphate excretion.

2. Medical need

Main causes of hyperphosphatemia are represented by acute and chronic renal failure, for a defect in urinary phosphate excretion.

In acute renal failure (ARF), hyperphosphatemia is characteristic in the oliguric and early diuretic phase, it is accentuated by acidosis and hypercatabolism and it is particularly severe in ARF secondary to rhabdomyolysis. In chronic renal failure (CRF), it becomes evident once the glomerular filtration rates declines < 40 ml/min/1.73 m², whereas in early renal failure, plasma phosphate is maintained in the normal range by an increase in parathyroid hormone (PTH) levels.

Other causes of hyperphosphatemia are hypoparathyroidism, acromegaly, tumor calcnosis or increasing phosphate intake such as phosphate-rich enema and laxatives and/or shift of phosphate from red blood cells and skeletal muscle cell lysis and treatment with vitamin D. In particular, patients with renal disease, who are routinely treated with a large dose of vitamin D for secondary hyperparathyroidism, may develop hypercalcemia and hyperphosphatemia, which can limit the use of a higher dose of vitamin D.

The phosphate increase, together with calcium increase is the major determinant in metastatic deposition. Indeed, a calcium-phosphorus product > 55 mg²/dl² (K/DOQI guideline on bone metabolism target levels for CRF) is considered the threshold, above which metastatic calcification occurs.

In the last few years, the control or reduction of phosphate levels in dialysis patients has become one of the main therapeutic targets in managing the vascular complication and reducing the cardiovascular mortality in end-stage renal disease (ESRD).

3. Existing treatment

The aim of management is to maintain plasma phosphate and consequently CaXP product in the normal range.

3.1 Dietary intervention

Dietary intervention to phosphate reduction, in patients with CRF, represents the first step. Its intake could be reduced by avoiding food rich in phosphate, such as milk, cheese, eggs, all meat (particularly liver, kidney and veal) and fish (particularly fatty fish such as salmon, trout shellfish etc.). However, dietary phosphate restriction cannot be undertaken without severely compromising protein intake and moreover it is in contrast with the minimum amount of protein (1.2 g/kg body weight/day) that is recommended in dialysis patients in order to prevent malnutrition. As each gram of protein contains 12 – 16 mg of phosphorus, in a subject of 70 kg, the amount of phosphate intake will normally be > 1200 mg/day. For this reason dietary phosphate prescription alone is not adequate to correct hyperphosphatemia.

3.2 Dialysis removal

Hemodialysis normally removes phosphate rapidly during the first hour as phosphate is cleared from the extracellular pool, thereafter, the rate of phosphate removal is limited by equilibration across the cell membrane. During a normal session of conventional intermittent haemodialysis – 900 mg of phosphorus are removed, which is not sufficient to keep the patient in neutral phosphorus balance. Lengthening dialysis time and increasing frequency dose are the best option for removal of phosphate during hemodialysis. Prolonged nocturnal dialysis has been demonstrated to reduce phosphorus levels better than short daily dialysis, but unfortunately such a modality of dialysis is difficult to perform in many dialysis units and consequently is not widely accepted. Peritoneal dialysis is also inadequate to remove phosphate ingested with a normal protein intake diet.

Therefore, as dietary intervention and dialysis removal often do not permit correction of hyperphosphatemia in hemodialysis patients, these intervention are usually combined with the prescription of phosphate binders in order to maintain serum phosphate levels within the normal physiologic range.

3.3 Phosphate binders

Due to the limited results obtained to correct hyperphosphatemia with dialysis or with diet, it became necessary to focus attention on other substances able to remove the excess of phosphate from the body. For this reason the majority of patients in dialysis or with an advanced stage of renal failure are treated with phosphate binders. The purpose of therapy with phosphate binders is either to limit the adsorption of dietary phosphate intake and to maintain phosphohormone within the normal physiologic range, according to the recommendation of the National Kidney Foundation (3.5 – 5.5 mg/dl). Commonly used phosphate binders are hydroxide, carbonate
or acetate salts of mineral ions (such as aluminum, magnesium, calcium or lanthanum). All these compounds act by binding phosphate in the gut; firstly they dissolve the metal ion, which is subsequently complexed with ingested phosphorus, thereby preventing the bound phosphorus from being adsorbed and eliminating it in the stool.

### 3.3.1 Aluminum-based binders

The aluminum-based binders (aluminum hydroxide and aluminum carbonate) were first introduced in 1970s for the treatment of hyperphosphatemia. Until the mid-1980s, aluminum-containing phosphate binders represented the main therapy for this disorder in dialysis patients. Aluminum is excreted mainly by the kidney, but due to their accumulation in CNS, bone and hematopoietic cells, aluminum may be dangerous when ingested chronically. This resulted accumulation leads to the development of dialysis-related encephalopathy [14], microcytic anemia, myopathy and osteomalacia [15], the last due to the effect of aluminum on one matrix mineralization and osteoblast activity. Aluminum accumulation and toxicity, especially in the past, was caused both by aluminum-based binders and by dialysis-water contamination. In particular, patients on dialysis may be more exposed to aluminum toxicity because plasma protein binding prevents their removal by dialysis filters [16]. Contemporary ingestion of aluminum compounds together with foods containing citric acid markedly increase gastro-intestinal aluminum adsorption and, therefore, its toxicity [17]. In selected cases, aluminum compounds may be used, but at the dose of 40 – 45 mg/kg/day, and should only be used for 4 – 8 weeks. For this reason, aluminum-binding agents are now commonly used occasionally, as a short-term therapy (days to weeks) and subsequently shifted to other phosphate binders.

### 3.3.2 Calcium-based binders

Because of the risk of aluminum toxicity, since the 1990s calcium carbonate and calcium acetate have replaced aluminum-based salts in clinical practice and represent the two most widely used preparations for the treatment of hyperphosphatemia. Calcium-based binders should be taken during or at the end of a meal to optimize their effect on phosphate. When these compounds are used to correct hypocalcemia they can also be taken between meals. The effect of calcium carbonate is linked with gastric pH and this should be taken into account when inhibitors of the protonic pump or related analogs are also administered. Indeed, an acidic gastric pH is optimal to dissolve calcium carbonate, for this reason the contemporary assumption of antiacidic drugs may reduce the efficacy of calcium carbonate. On the contrary, a higher pH is necessary for the binding capacity of calcium to phosphorus. For these reasons, calcium salts have less efficacy than aluminum salts.

Unfortunately, high doses of calcium carbonate are required to reduce serum phosphorous (average of 6 g/day up to 10 or even 15 g/day) to acceptable levels due to the lower phosphate binding capacity of these compounds [18]. This leads to another major problem, which is hypercalcemia, and it is related to the high levels of ingested calcium. Approximately a third of patients using calcium carbonate have elevated levels of serum calcium [19]. The consequence to this disorder is a positive calcium balance with a large amount of unbound calcium that may determine soft tissue calcification, especially when plasma phosphate is elevated for an increase of Ca×P product (see Section 1).

In fact, coronary artery calcification may develop and it contributes to the increased risk of cardiovascular morbidity and mortality of ESRD patients [2]. In young adults with ESRD, the intake of calcium was directly correlates with the coronary artery calcification scores determined by electron beam computed tomography. A study that evaluated vascular calcification by ultrasonography, reported the same direct correlation between calcium intake and calcium deposition in vessels [1]. London et al., demonstrated a higher degree of arterial media calcification in dialysis patients with a higher intake of calcium-based binders, compared with patients without vascular calcifications (2.2 g versus 1.1 g; p < 0.01) [20].

Another complication of calcium carbonate is adynamic bone disease. This bone disease, which in ~50% of cases is due to aluminum toxicity, may be due to the result of an oversuppression of PTH. This disorder, was first described in pediatric patients on dialysis and subsequently in other studies [21,22]. The main findings of this state of low bone turnover disease are an increase in serum calcium, PTH suppression and low levels of alkaline phosphate. Some authors reported a correlation between adynamic bone disease, studied by histomorphometry, and arterial calcification [23]. For this reason, the K/DOQI guideline for bone and mineral metabolism recommended a maximum dose of elemental calcium intake, from the use of calcium-based binders, which should not exceed 1.5 g/day [24].

In addition, the need of vitamin D supplements for the treatment of hyperparathyroidism, joined with the treatment with calcium-based phosphate binders may oversuppress PTH and increase calcium absorption [25].

Another calcium-based phosphate binder is calcium acetate. It achieves similar phosphate binding effects as calcium carbonate at a lower dose of calcium (nearly 50%), and its solubility is independent of the level of pH and the incidence of hypercalcemia is smaller compared with calcium carbonate [26]. Calcium acetate has been shown to possess better binding ability than calcium carbonate due to a better solubility and consequently smaller calcium absorption, which leads to fewer hypercalcemic events that are the starting point for a dangerous long-term complication such as vascular calcification.

Calcium citrate, another calcium-based binder, is less effective because citrate competes with phosphorus for binding with calcium. Moreover, especially in dialysis patients treated with aluminum-containing compounds, calcium
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citrate should be avoided as it favors intestinal aluminum absorption and, therefore, aluminum intoxication [27].

3.3.3 Magnesium-based binders
Magnesium-based binders (magnesium hydroxide and magnesium carbonate) represent an alternative treatment to calcium-based binders for hyperphosphatemia [28]. Compared with calcium carbonate or calcium acetate, magnesium salt are less effective and for this reason larger doses are needed with frequent development of side effects like hypermagnesemia, hyperkalemia and gastrointestinal disorders such as diarrhea. Due to the occurrence of these complications, magnesium hydroxide and magnesium carbonate are less frequently used compared with calcium-based binders [29].

3.3.4 Sevelamer hydrochloride
Sevelamer hydrochloride is a non-absorbed, cationic polymer with a phosphate binding action and no calcium or aluminum [30]. It is intended to be taken orally in divided doses with meals. Sevelamer acts in the small intestine and its maximum effect on phosphate binding occurs at pH 6 or 7. As the absorption of phosphate is not significant in the stomach and at the beginning of the small intestine, where the pH is low, the clinical relevance of this absence of phosphate binding capacity at low pH is minimal. The side effect of sevelamer intake is metabolic acidosis, due to the release of chloride ions in the process of binding phosphate and bicarbonate, thereby resulting in the net absorption of a proton. This will cause a decrease of 2 – 3 mEq/l in serum bicarbonate.

It has been observed that the molecule sevelamer is able to effectively reduce phosphate plasma levels in ESRD patients under dialysis both in preclinical phase studies and in clinical application without increasing serum calcium levels [31-33]. In spite of these evidences, significant controversy has emerged due to the results of several studies comparing calcium binders with sevelamer and their effect on phosphate removal. In particular, in the CARE (Calcium Acetate Renagel Evaluation) study, a randomized, double-blind trial comparing sevelamer with calcium product showed that calcium acetate produced a better control of hyperphosphatemia, even if in the sevelamer group hypercalcemic episodes were less frequent and the dose of sevelamer was below the therapeutic dosage and not equivalent to the dose of calcium acetate [34]. The reduced incidence of hypercalcemia in patients treated with sevelamer allows treatment with higher doses of calcitriol for a better control of the secondary hyperparathyroidism. Collins et al., in a case control study, showed a reduction in hospitalization risk, compared with control patients for a mean follow up of 17 months [35].

Moreover, as an additional benefit, sevelamer has been shown to remarkably reduce the serum level of low density lipoprotein [35], increase high density lipoprotein by ~20% and decrease PTH. Very recently, sevelamer was observed in an animal model to reduce the parathyroid gland weight with a reduction in serum PTH levels by means of regression of cell hypertrophy [36]. The attenuation of vascular and, in particular, coronary calcifications of sevelamer, compared with calcium based phosphate binders in ESRD patients under dialysis, has been studied by electron beam computed tomography [37,38]. In particular, in the TTG (Treat to Goal) study, sevelamer showed, at 6 months and at 1 year, a lower calcification score in coronary arteries and aorta (using electron beam computed tomography) of 200 hemodialysis patients, compared with patients treated with calcium-based phosphate binders [39]. However, it has to be noted that it is not completely established whether or not the effect of sevelamer on arterial calcification reflects its role as a phosphate binder or is the main result of its lipid-lowering effect. In any case sevelamer represents a step forward in the management and treatment of hyperphosphatemia. The RIND (Renagel in New Dialysis) trial, has shown that treatment with sevelamer significantly reduces serum phosphorus levels in incident patients on hemodialysis, with less incidence of hypercalcemia compared with calcium-based binders [40]. Moreover, recently it was demonstrated that treatment with sevelamer was associated with a significant reduced mortality as compared with the use of calcium-containing phosphate binders [41]. High doses of sevelamer (3.2 – 8 g/day) are necessary to bring hyperphosphatemia back to target level and the number of pills per day (~ 8 × 800 mg tablets) may certainly be a conditioning factor for compliance of the patient. Given the high cost of sevelamer compared with the traditional phosphate binders, the association of sevelamer with other binders may be an interesting solution for the patients, in order to reduce the amount of calcium and aluminum improving their compliance and reduce the cost of the therapy. In particular the association of sevelamer allows a reduction in dosage of calcium-based binders, as the last K/DOQI guidelines for bone and mineral metabolism recommended the use of a maximal dose of 1.5 g of elemental calcium as calcium-based binders [24]. Recently, it has been shown in a group of hemodialysis patients that treatment with sevelamer was associated with antiatherogenic and anti-inflammatory effects characterized by reduction in total and low-density lipoprotein cholesterol, apolipoprotein B and high sensitivity C-reactive protein [42].

3.3.5 Lanthanum carbonate
In 2004, the US FDA approved another substance, lanthanum carbonate, for the treatment of hyperphosphatemia in patients on dialysis. Lanthanum carbonate, is a calcium and aluminum free compound that has been shown to possess similar phosphate binding activity to aluminum, with the advantage of a minimal absorption [43]. The activity as a phosphate binder of lanthanum carbonate is very specific with an optimal binding that ranges from pH 3 to 5. Lanthanum is not metabolized and its absorption is extremely low with consequently extremely low retention in tissues. It is eliminated by way of bile (80%) and high amounts of ingested lanthanum are eliminated in the feces; therefore, it is not accumulated in
tissues of patients with reduced renal function. Patients with ESRD treated with lanthanum carbonate, with a dose in the range of 1500 – 3000 mg/day, reported similar phosphate controls to calcium-based phosphate binders in patients on dialysis, but with a lower incidence of hypercalcemia. It is well tolerated, with few side effects, characterized by gastrointestinal symptoms: nausea, vomiting, diarrhea and abdominal pain.

An experimental study performed on rat models showed equivalence of lanthanum compared to aluminum binders, but it was superior when compared with calcium phosphate binders [44].

Patients with ESRD treated with lanthanum carbonate ≤ 2.5 – 3.8 g/day for 3 – 4 weeks, have been reported to obtain effective reduction of serum phosphorous level. In the same study, treated patients have also been shown to reach a significantly reduced calcium/phosphate product and PTH level compared with placebo [45]. Hypercalcemia was not associated with treatment and adverse effects were comparable with those recorded in the placebo group. Therefore, lanthanum carbonate is as well tolerated and as effective as calcium carbonate as a phosphate binder [46].

The major concern regarding the use of this drug was the possible deposition of lanthanum in bone and other tissue, especially after the experience with aluminum. In a 12-month bone biopsy study, patients treated with lanthanum carbonate versus calcium carbonate were studied for the evolution toward normal bone histomorphometric parameters. This study showed less episodes of hypercalcemia in the lanthanum group and no progression toward low-turnover bone disease and no evidence of bone complications associated with aluminum-based phosphate binders [47]. Some experimental studies showed that lanthanum may accumulate in tissue. In particular, it was demonstrated that administration of lanthanum to rats for many days (28 – 110 days) was associated with accumulation in several tissues including lung, kidney, bone and especially in the liver. [48,49]. In particular, as the liver is the main route of excretion for lanthanum carbonate, in a study on rats, lanthanum liver accumulation was investigated by advanced transmission electron microscopy techniques. With this technique, lanthanum was localized in the lysosomes of hepatocytes, but it was not detected in other surrounding cellular components [50].

Recently, the effect on PTH gene expression was examined. Uremic rats treated for 4 weeks with lanthanum carbonate showed control of hyperphosphatemia and hyperparathyroidism and decrease of PTH gene expression, without hepatic toxicity as shown by biochemical, imaging and light microscopy studies on the liver [51].

Data, so far obtained, showed a substantial equal effect between lanthanum and other calcium-based binders with the advantage of less incidence of hypercalcemia, which is an advantage obtained with the use of this compound. Finally, findings in human and animal studies, especially for those concerning potential toxicity associated with lanthanum accumulation in tissue, reveal a need for further investigation in order to determine the long-term consequences of lanthanum carbonate in patients with chronic renal failure.

4. Current research goals

Recently the authors’ group studied the phosphorus content of salivary secretions and salivary phosphate secretion in...
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ESRD patients. Salivary fluid contains electrolytes including phosphate [52], which if related to the amount of salivary secretion per day, may raise interest in identifying another possible approach to phosphorus removal in uremic patients. Normal salivary secretion is known to be in the range of 1000 – 1800 ml/day [52]. The authors evaluated salivary phosphate secretion in a group of ESRD patients under chronic dialysis treatment compared with healthy subjects used as a control group [53].

The authors observed that the salivary phosphorus ratio in hemodialysis (HD) patients is more than doubled and salivary phosphorus is five-times higher than serum phosphorus compared with healthy controls. In addition, in HD patients, salivary phosphorus correlated with serum phosphorus and multivariate

![Figure 2. Molecular mechanism for salivary secretion: A) acinous cell; and B) acinous gland.](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Chemical structure</th>
<th>Indication</th>
<th>Development stage</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate</td>
<td>Fresenius</td>
<td>Calcium acetate</td>
<td>Hyperphosphatemia</td>
<td>Launched in Canada and US Preregistration in Europe</td>
<td>Phosphate binder</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Several companies</td>
<td>Calcium carbonate</td>
<td>Hyperphosphatemia</td>
<td>Launches</td>
<td>Phosphate binder</td>
</tr>
<tr>
<td>Sevelamer hydrochloride</td>
<td>Genzyme</td>
<td>2-Propen-1-amine polymer with (chloromethyl)oxirane, hydrochloride</td>
<td>Hyperphosphatemia</td>
<td>Launched</td>
<td>Phosphate binder (it binds dietary phosphorus from the gastrointestinal tract without being absorbed into the bloodstream and prevents phosphorous absorption in the small intestine)</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>Shire</td>
<td>Carbonic acid, lanthanum (3+) salt</td>
<td>Hyperphosphatemia</td>
<td>Launched</td>
<td>Phosphate binder (it has a high affinity for phosphate and exhibits little systemic absorption)</td>
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| Calcium acetate + magnesiu
mucifer carbonate          | Fresenius       | Calcium acetate and magnesium carbonate                                           | Hyperphosphatemia      | Launched                                 | Phosphate binder                                                                  |
| Alusulf                   | Madaus          | Aluminum hydroxide sulfate, dodecahydrate                                          | Hyperphosphatemia      | Launched                                 | Phosphate binder                                                                  |

Table 1. Competitive environment table for approved phosphate binders.
Table 2. Competitive environment table for phosphate binders under clinical investigation.

<table>
<thead>
<tr>
<th>Compound</th>
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<th>Indication</th>
<th>Development stage</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer carbonate</td>
<td>Genzyme</td>
<td>A second-generation analog of sevelamer hydrochloride</td>
<td>Hyperphosphatemia</td>
<td>Australia: Phase III clinical trial US: preregistration</td>
<td>Phosphate binder</td>
</tr>
<tr>
<td>Colestilan</td>
<td>Mitsubishi Pharma</td>
<td>Colestimide</td>
<td>Hypercholesterolaemia</td>
<td>Launched Phase II clinical trial Phase II clinical trial</td>
<td>Phosphate binder (it is a bile acid sequestrant resin, developed for hypercholesterolaemia)</td>
</tr>
<tr>
<td>Phosphate binders</td>
<td>Non-industrial source</td>
<td>Guanidine crosslinked polymers</td>
<td>Renal failure</td>
<td>UK: Phase II clinical trial</td>
<td>Phosphate binder</td>
</tr>
<tr>
<td>RenaZorb</td>
<td>Altair Nanotechnologies</td>
<td>A nanoparticle-sized lanthanum-containing compound</td>
<td>Hyperphosphatemia</td>
<td>Preclinical (US)</td>
<td>Phosphate binder (it removes phosphate ions from patients with end stage renal disease undergoing kidney dialysis)</td>
</tr>
<tr>
<td>Alpharen</td>
<td>Vectura</td>
<td>Chemical protein not containing aluminium or calcium ions</td>
<td>Hyperphosphatemia</td>
<td>UK: Phase II clinical trial</td>
<td>It shares the characteristics of insoluble hydrotalcite structures and aluminum-based hydrotalcites are available as antacids</td>
</tr>
<tr>
<td>ILY-101</td>
<td>Amgen</td>
<td>Metal-free polymer</td>
<td>Hyperphosphatemia</td>
<td>Phase II clinical trial</td>
<td>Phosphate binder (it binds to phosphorus in the gastrointestinal tract)</td>
</tr>
<tr>
<td>SBR-759 (Seboren)</td>
<td>Novartis</td>
<td>Polynuclear iron (Ⅲ) starch/saccharose complex</td>
<td>Hyperphosphatemia</td>
<td>Switzerland: Phase I clinical trial</td>
<td>It binds selectively to phosphate ions through chelation</td>
</tr>
<tr>
<td>Zerenex</td>
<td>Keryx Biopharmaceuticals</td>
<td>Inorganic, iron-based compound</td>
<td>Hyperphosphatemia</td>
<td>Phase II clinical trial</td>
<td>Phosphate binder (it is attached to a citrate ion)</td>
</tr>
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</table>

analysis confirmed that serum phosphorus was the only independent factor predicting increased salivary phosphorus secretion (Figure 1). Salivary glands share some physiologic similarities with renal structures that may open new perspectives in evaluating phosphate disorders in uremic patients. Indeed, secretory units of salivary glands are clusters of cells called acini and their function is similar to that of renal tubules. The acini, in fact, secrete a primary salivary fluid that contains water, electrolytes, mucus and enzymes, which flow into the collecting ducts where the composition of saliva is managed. Sodium is actively reabsorbed whereas potassium and phosphate are secreted. In HD patients, the increased salivary secretion, and that of salivary phosphate in particular, could be a rational explanation for the compensatory activity of the salivary glands increasing their secretion in the presence of impaired kidney function. The effect of this compensatory secretion is, however, abolished by the ingestion of saliva and following absorption in the intestinal tract there may become a vicious circle between salivary phosphate secretion and fasting phosphate absorption, thereby worsening hyperphosphatemia. The demonstration that salivary phosphate secretion in the authors’ HD patients is increased could open an important path for a possible additional therapeutic approach to hyperphosphatemia by breaking the vicious circle caused by the absorption of the increased salivary phosphate. In fact, by knowing the salivary phosphate balance in HD patients, it could be possible to bind salivary phosphate secretion, reducing its absorption and, therefore, further reducing the serum phosphate concentration.

5. Scientific rationale

The authors’ data are supported by the evidence that secretory units of salivary glands are a cluster of cells called acinous and their function has a similarity with the function of renal tubules (Figure 2). The acinous cells, in fact, secrete a primary salivary fluid that contains water, electrolytes, mucus and enzymes, which flows out into collecting ducts where the composition of saliva is managed. Sodium is actively reabsorbed whereas potassium and phosphate are secreted. In HD patients the increased salivary secretion, and that of salivary phosphate in particular,
could find a rational explanation in the compensatory activity of the salivary glands that increase their secretion in the presence of an impaired kidney function. The effect of this compensatory secretion is, however, abolished by the ingestion of saliva in the intestinal tract that may result in a vicious circle between salivary phosphate secretion and fasting phosphate absorption, therefore, worsening hyperphosphatemia.

6. Competitive environment

Hyperphosphatemia is a target of many drugs, which act to different extents as binding agents. This paper focuses on already launched phosphate binders. For this reason the authors constructed two different tables: Table 1 lists the approved phosphate binders and Table 2 lists the drugs that are still under clinical investigation and that are not treated in detail in this manuscript.

7. Potential development issue

The demonstration that salivary phosphate secretion in HD patients and chronic renal failure is increased, could help to open a new important way for a possible additive therapeutic approach to hyperphosphatemia through the breaking of the vicious circle realized by the ingestion of the increased salivary phosphate. As salivary mucous phosphate concentration in uremic patients reflects serum phosphate level, it could be possible, for example, to bind salivary phosphate secretion to reduce its absorption and reduce serum phosphate concentration. This attractive therapeutic implication will clearly need investigations in order to both identify substances for their use as salivary phosphate binders and evaluate the identified substances in a clinical setting, which requires further clinical studies.

Colestamide, which presently is being used for hypercholesterolemia was found to reduce serum phosphate level. The mechanism of action of colestamide is not clear, but because of its similar structure with sevelamer, authors consider that it may work as a phosphate binder in the same way, with similar clinical effects (54).

Stabilized polynuclear iron idroxide is a new compound that has shown remarkable in vitro phosphate binding capacity. It is an insoluble polynuclear iron hydroxide that acts through a formation of an iron–phosphate complex. Although the study of this compound is still in the preclinical stage (55), this compound has demonstrated a comparable phosphate binding efficacy to other non-calcium, non-aluminum phosphate binders. However, the long-term safety with respect to iron release and to potential interaction with absorption of micronutrients requires further investigations.

8. Expert opinion

Cardiovascular calcifications are known to contribute greatly to the increased morbidity and mortality of ESRD and HD patients (1) and hyperphosphatemia is recognized as playing a causative role in the induction of these complications (1-6). Pharmacologic therapeutic approaches to hyperphosphatemia in ESRD patients are based only on phosphate binders, which together with reduced dietary phosphate intake, join dialysis to remove excess phosphorus from the blood. Patient incompliance represents the major reason for failed treatment (56).

Aluminum compounds may be used in selected cases at the dose of 40 – 45 mg/kg/day and as a short-term therapy (only for 4 – 8 weeks) and subsequently shifted to other phosphate binders. At present, their long-term use is not employed due to their serious adverse effects.

Calcium-containing binders are still the most common drugs employed to correct phosphate serum levels, especially in patients with hypocalcemia. If given during meals, calcium-binders have a hypophosphatemic effect, whereas if given far from meals they only increase calcium levels. It must be remembered that calcium-binders carry a positive calcium balance that may determine vascular calcification, especially when plasma phosphate is elevated (> 5.5 mg/dl) through an increase of CaXP product. For this reason, the K/DOQI guideline for bone and mineral metabolism recommended a maximum dose of elemental calcium intake, from the use of calcium-based binders, which not should exceed 1.5 g/day (24).

The contemporary treatment with vitamin D supplements for hyperparathyroidism may increase calcium absorption and, therefore, it must be used with caution.

Sevelamer hydrochloride represents the first non-calcium, non-aluminum-based binder and has shown effective control of serum phosphorus. Several pills per day (~ 8 × 800 mg tablets) are necessary to bring hyperphosphatemia back to target level and may certainly be a conditioning factor for compliance of the patient. Moreover, in addition to the action of phosphorus removal, sevelamer has been shown to result in significant reduction in serum low-density lipoprotein cholesterol and low-density:high-density lipoprotein cholesterol ratio in dialysis patients.

Lanthanum carbonate is another calcium-free option for effective management of hyperphosphatemia. Compared with calcium-based binders, it offers the same advantage on phosphate without carrying a positive calcium balance. Tissue metal deposition may represent a limit for long-term treatment especially in young patients on dialysis. Long-term safety data are needed in order to exclude potential adverse effects correlated to their tissue deposition.

Despite these therapeutic measures, > 50% of patients still have serum phosphate levels above the range recommended by the K/DOQI guidelines and only 5% of all dialysis patients achieve all four of the K/DOQI goals for mineral metabolism (57). Therefore, it is very important to identify new methods of intervention and other possible therapeutic approaches to reduce phosphate levels in blood.
Bibliography

Papers of special note have been highlighted as of considerable interest (*) to readers.


29. DELMEZ JA, KELBER J, NORWOOD KY, GILES KS, SLATOPOLSKY E: Magnesium carbonate as a phosphorus binder: a prospective,
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35. This study provides evidence that in patients with CKD stage 5D, as in the uremics, coronary artery calcification is associated with a worse outcome.
49. A new attractive therapeutic implication for the use of salivary phosphate binders.


Affiliation
Guido Bellinghieri, Domenico Santoro† & Vincenzo Savica
†Author for correspondence
University of Messina,
Division of Nephrology and Dialysis,
Policlinico Universitario,
Viale Gazzi – 98100, Messina, Italy
Tel: +39 090 2212339; Fax: +39 090 2925899;
E-mail: santisi@unime.it