Phosphate Binding Agents
Drug Class Review

40:18.19 Phosphate-Removing Agents

Calcium Acetate (Calphron® [OTC]; Eliphos®; PhosLo®; Phoslyra®)
Lanthanum (Fosrenol®)
Sevelamer (Renagel®; Renvela®)

Final Report
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Executive Summary

Introduction: The phosphate binding agents are indicated in the reduction of hyperphosphatemia in end-stage renal disease. Several phosphate binding agents are currently available for use in the United States. This review focuses on calcium acetate (the most commonly used calcium salt) and the new non-calcium phosphate binders: lanthanum (Fosrenol®) and sevelamer (Renagel®; Renvela®). All included agents are available in oral formulations and must be administered with food to be effective.

Chronic kidney disease (CKD) is a condition which affects over 20 million Americans and the incidence is rapidly rising. CKD is defined as a long-standing decline in renal function with progressively decreasing glomerular filtration rate. The goal of therapy in CKD is to slow the progression and to treat complications. Current Kidney Disease Practice Guidelines (KDIGO, 2012) support the prevention of hyperphosphatemia with phosphate binders in patients with CKD but do not recommend one agent over another.

Clinical Efficacy: The phosphate binding agents were evaluated in eight clinical trials and one meta-analysis involving a total of 68 clinical trials and over 12,000 patients. According to the clinical evidence, the phosphate binding agents are more efficacious than placebo in reducing serum phosphorous levels. No differences in reduction of phosphorous levels were reported between calcium acetate, lanthanum or sevelamer. One trial reported an increased reduction in mortality with sevelamer therapy in those over the age of 65. Overall, clinical evidence demonstrates similar rates of efficacy between sevelamer, lanthanum and calcium acetate therapy.

Adverse Drug Reactions: The most common adverse effect reported with the agents is gastrointestinal upset, including nausea, vomiting, and diarrhea. In clinical trials, hypercalcemia was reported more frequently in patients taking calcium acetate and gastrointestinal upset was reported more frequently in patients taking sevelamer. Current clinical practice guidelines recommend reducing or restricting the dose of calcium based phosphate binders, like calcium acetate, in patients with persistent hypercalcemia.

Summary: Overall, the phosphate binding agents are safe and efficacious in the reduction and prevention of hyperphosphatemia in patients with CKD. Choice of agent should be based on individual patient characteristics, phosphate and calcium consumption, lab values, tolerability, and cost.

Introduction

Several phosphate binding agents are currently available for use in the United States. Calcium-containing salts bind phosphorus and may be used to slow or prevent renal bone disease. This review will focus on calcium acetate (the most commonly used calcium salt) and the new non-calcium phosphate binders: lanthanum (Fosrenol®) and sevelamer (Renagel®; Renvela®). The phosphate binding agents are indicated in the reduction of hyperphosphatemia in end-stage renal disease. All included agents are available in oral formulations and must be administered with food to be effective. Table 1 provides a summary of the agents.

Disease Overview

Chronic kidney disease (CKD) is a condition which affects over 20 million Americans. The incidence of CKD has more than doubled since 2000 and is increasing most rapidly in Americans over age 65. CKD is defined as a long-standing decline in renal function with progressively decreasing glomerular filtration rate (GFR).[3] CKD is typically diagnosed after the presence of reduced renal function over a period of at least three months with demonstrated irreversibility.[4] Common etiologies include chronic, uncontrolled hypertension and diabetic nephropathy, secondary to diabetes mellitus.[3] The goal of therapy in CKD is to slow the progressive decline in renal function and to treat complications associated with the disease.[3] CKD is staged based on estimated GFR with stage 1 defined as GFR ≥ 90 mL/min and stage 5 defined as GFR < 15 mL/min.[4] End stage renal disease (ESRD) is the point at which kidney impairment is irreversible and usually requires dialysis or kidney transplant.[3] Population survey data estimates at least 6% of the US population has CKD stages 1 and 2 and an additional 4.5% has stages 3 and 4.[3] Overall costs per person per year for a patient age 65 and older with CKD were estimated at $22,323 in 2010.[5]

Several complications of CKD include worsening of cardiovascular disease, anemia, hypoalbuminemia, hyperparathyroidism, metabolic acidosis, 25(OH)-vitamin D deficiency, and other electrolyte disorders.[3] Hyperphosphatemia is an electrolyte disorder affecting about 23% of those with GFR < 30mL/min.[4, 6] Phosphate, calcium, and parathyroid hormone are all inter-related in patients with CKD and important to maintaining proper bone health.[4] A recent systematic review demonstrated that all-cause mortality increases by 18% for every 1 mg/dL increase in serum phosphate concentration, with an increased risk of cardiovascular mortality as well.[7] Prevention of hyperphosphatemia is an important clinical endpoint to treat in patients with CKD.

The phosphate binding agents are FDA-labeled for use in hyperphosphatemia secondary to CKD.[8] Current Kidney Disease Guidelines (KDIGO, 2012)[4] support the prevention of hyperphosphatemia with phosphate binders in patients with CKD. The guidelines do not recommend any of the available phosphate binding agents over another. In the absence of hypercalcemia, it may be preferred to use one of the more inexpensive calcium-based agents. Variation in phosphate and calcium consumption, individual lab

values, tolerability of different agents, and cost may impact which option is best for an individual patient. The available agents listed in the guidelines include: aluminum hydroxide, calcium citrate, calcium carbonate, calcium acetate, calcium acetate with magnesium carbonate, lanthanum carbonate, sevelamer hydrochloride, and sevelamer carbonate. Aluminum has been used extensively; however, evidence of long-term use resulting in accumulation in bone and neural tissue has limited its use. This accumulation can cause osteomalacia and may contribute to various neurological conditions, such as Alzheimer's disease.[9] Any of the calcium products may adversely increase the serum calcium level, with calcium acetate impacting the serum levels to a lesser degree. Lanthanum avoids effects on calcium, but may accumulate in bone and other tissues with long-term use. Sevelamer does not affect calcium levels and has extensive clinical trial data to support its use.[4] In patients who do not have hypercalcemia, it may be preferred to use the calcium-based phosphate-binders due to their cost-effectiveness.[4]

Table 1. Comparison of the Phosphate Binding Agents[1, 2]

Agents	How supplied	Labeled Indications	Clinical Considerations	Generic/ Manufacturer
Calcium Acetate (Calphron® [OTC]; Eliphos®; PhosLo®; Phoslyra®)	Oral Capsule: 667mg Oral Tablet: 667mg Oral Solution: 667mg/5mL (473mL) [**contains methylparaben, propylene glycol]	Control of hyperphosphatemia in end-stage renal failure	Calcium acetate 667mg = elemental calcium 169mg = calcium 8.45mEq = calcium 4.23mmol Initial Dosing: 1,334mg/meal (2 tablets/meal) Maintenance Dosing: 2,001-2,668mg/meal (3-4 tablets/meal) Must be administered with meals to be effective Does not promote aluminum absorption	Yes; tablet & capsule No; solution; Hawthorn Pharmaceuticals
Lanthanum (Fosrenol®)	Chewable Tablet: 500mg, 750mg, 1000mg	Reduction of serum phosphate in patients with end-stage renal disease [ESRD], kidney failure (GFR <15 mL/minute/1.73 m2 or dialysis)	Initial Dosing: 1,500mg/meal (2 tablets/meal) Maintenance Dosing: 1,500-3,000mg daily in divided doses given with meals (1-2 tablets/meal) Administer with or immediately after meals Tablet should be chewed completely prior to swallowing; not swallowed whole	No; Shire US
Sevelamer (Renagel®; Renvela®)	Oral packet, as carbonate: 0.8g (1ea, 90ea); 2.4g (1ea, 90ea) [citrus flavor] Oral tablet, as carbonate: 800mg Oral tablet, as hydrochloride: 400mg, 800mg	Reduction or control of serum phosphorous in patients with chronic kidney disease on hemodialysis	Renagel: Initial & Maintenance: 800-1,600mg/meal Renvela: Initial: 800–1,600mg/meal (1-2 tablets/meal) Maintenance: 1,600–2,400mg/meal (2-3 tablets/meal) Must be administered with meals Drink within 30 minutes of preparing Tablets must be swallowed whole; do not crush	No; Renagel® & Renvela®: Genzyme

Mechanism of action

The phosphate binding compounds work by reducing the bioavailability of dietary phosphate in the gastrointestinal tract. The mechanism of phosphate binding for each of the phosphate binding agents is similar. The agents exploit the anionic nature of phosphate and use ionic interactions to attract, bind and precipitate phosphate out of solution. The insoluble phosphate compound is ultimately excreted in the feces.[10-12] Sevelamer is composed of a cationic hydrogel which is insoluble in water and has multiple amine groups which becomes protonated in the gastrointestinal tract and bind to the anionic phosphate.[13] As a nonselective anion exchange, sevelamer also binds other anionic substances such as bile acids and some medications which can cause decreased absorption and serum levels of certain medications. Calcium acetate and lanthanum are salts that dissociate to from cations which bind the phosphate anions to form insoluble precipitates. None of the agents have extensive systemic absorption. Up to 40% of the elemental calcium in calcium acetate may be absorbed if taken on an empty stomach. Less calcium is absorbed if taken with meals. Lanthanum has less than 0.002% system absorption and sevelamer has not demonstrated any systemic absorption.[14, 15]

Methods

A literature search was conducted to identify articles addressing clinical safety or efficacy of the phosphate binding agents, searching the MEDLINE database (1950 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 10/2013, evaluating efficacy of the agents are included. Trials evaluating the phosphate binding agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than one reason):

- Clinical trials which evaluated pharmacokinetic studies, pharmacodynamic studies, adverse effects studies, in vivo studies, adherence analyses and cost analyses
- Individual trials involving indirect comparison analyses
- Trials involving dose-finding studies or in indications other than the approved indications for the agent
- Individual clinical trials evaluating agents or formulations not currently available in the US or without full access to the article

Clinical Efficacy

The phosphate binding agents were evaluated in eight clinical trials and one meta-analysis involving a total of 68 clinical trials and over 12,000 patients. According to the clinical evidence, the phosphate binders are more efficacious than placebo in reducing serum phosphorous levels. Differences may exist in reductions in mortality, hospitalizations, and other secondary outcomes. See the evidence table in the appendix for a summary of all available evidence.

Navaneethan et al[25] conducted a meta-analysis of 60 clinical trials involving over 7,000 patients. All phosphate binders were found to be superior to placebo in reducing serum phosphorous levels. Calcium-based products led to higher calcium levels. Sevelamer was associated with an increased risk of GI upset compared to the calcium-based binders. Overall, the evidence was insufficient to support comparative superiority of any phosphate binder over another in reducing patient mortality or cardiovascular outcomes.

Block et al[26] evaluated lanthanum carbonate, sevelamer carbonate, and calcium acetate in 148 patients with CKD and normal serum phosphorous levels. Patients were randomly assigned to one of the treatment arms or placebo. All three phosphate binders were found to significantly decrease phosphorous levels relative to placebo. Calcium acetate had the most significant decline in parathyroid hormone versus placebo as compared with the other active agents. More gastrointestinal adverse effects were reported in the active treatment arms. In addition, an increase in vascular calcifications was seen with all agents, particularly calcium acetate.

Kasai et al[27] compared treatment with lanthanum carbonate to treatment with sevelamer hydrochloride in 42 patients with CKD on hemodialysis for at least three months. Patients were randomized to each of the agents in a crossover design with 13 weeks in each treatment arm. Serum calcium levels were similar for both treatment groups. Serum phosphate levels were lower with lanthanum therapy. Treatment-related adverse events were reported in 56% of the sevelamer group and 39% of the lanthanum group ($p<0.05$). Overall, the most common adverse effects reported in the study included constipation, flatulence, and dyspepsia.

Gulati et al[28] studied sevelamer hydrochloride and calcium acetate in 19 pediatric patients aged 2-18 with CKD stages 3 or 4. Patients were randomly assigned to either treatment arm for a period of 12 weeks. The adjusted mean phosphate levels at week 12 were not significantly different between treatment groups (5.3 vs. 6.1 mg/dL, $p=0.6$). Calcium levels were significantly lower in the sevelamer treatment group compared to the calcium acetate treatment group (8.2 vs. 9.1 mg/dL, $p=0.01$). No treatment-related adverse effects were reported in the sevelamer treatment arm.

Wilson et al[29] conducted a large trial of lanthanum carbonate compared to standard therapy in 1,354 patients on hemodialysis. Standard therapy was defined loosely as a phosphate binder other than lanthanum carbonate. Patients were randomized 1:1 to each arm and followed for up to two years. The primary outcome was survival, defined as time from first dose to all-cause mortality or last contact. Serum phosphorous levels were similar across treatment groups. At follow up, 19.9% of lanthanum patients and 23.3% of those on standard therapy had died; this difference in survival rate was small and did not reach statistical significance ($p=0.18$). In patients older than 65, the difference in survival rate was statistically significant; 27% of those on lanthanum had died compared with 39.3% of those on standard therapy ($p=0.04$). Overall, patients had similar survival outcomes in both groups, with a benefit in those over 65 years taking lanthanum compared to standard therapy.

St. Peter et al[30] evaluated sevelamer hydrochloride and calcium-based phosphate binders in 1,947 patients over 18 years who had been on hemodialysis for at least three months. This

study was a secondary analysis of data available from the Centers for Medicaid and Medicare Services (CMS). When comparing rates of hospitalizations and mortality, neither sevelamer nor calcium-based phosphate binders held an advantage. In the safety analysis, patients discontinued sevelamer more often and prescribers discontinued calcium-based products the majority of the time. GI side effects were associated more frequently with sevelamer therapy and the calcium-based products produced more hypercalcemia.

Delmez et al[31] compared sevelamer carbonate to sevelamer hydrochloride in 79 patients receiving hemodialysis. Patients were randomly assigned in double-blind fashion to either treatment arm, with a crossover occurring after 8 weeks. The two versions of sevelamer were equivalent in controlling serum phosphorous. Fewer patients experience GI side effects with the carbonate salt form of sevelamer compared to the hydrochloride salt formulation.

Suki et al[32] studied sevelamer hydrochloride and calcium-based phosphate binders in 1,068 patients over 18 years who had been on hemodialysis for at least three months. Patients were randomly assigned to each treatment arm across multiple study sites. No differences in efficacy we reported between treatment groups. In a sub group analysis of patients over the age of 65, sevelamer demonstrated superiority over calcium-based products in decreasing mortality. Patients on sevelamer experienced more GI side effects than those on calcium-based products.

Qunibi et al[33] evaluated treatment with calcium acetate compared to sevelamer hydrochloride in 100 adults on hemodialysis for longer than three months and receiving a stable dose of the phosphate binder and intravenous vitamin D for longer than one month. Patients whose serum phosphate rose above 6 mg/dL after 1-3 weeks of discontinuing the phosphate binder were included in the study. Calcium acetate was more effective in lowering serum phosphate levels compared to sevelamer. The rate of adverse effects was similar across treatment arms.

The phosphate binding agents were evaluated in eight clinical studies and one meta-analysis. Overall, sevelamer, lanthanum, and calcium acetate were found to be similar in efficacy. One study reported a reduction in mortality with sevelamer in a subgroup analysis of those over the age of 65. Hypercalcemia was reported more frequently in patients taking calcium acetate and GI upset was reported more frequently in patients taking sevelamer. Provider-based discontinuation was more common with calcium acetate and patient-based discontinuation was more common with sevelamer.

Adverse Drug Reactions

The phosphate binding agents are generally well tolerated. The most common adverse effect of reported with the agents is gastrointestinal upset including nausea, vomiting, and diarrhea.[16] Sevelamer is associated with the highest rate of gastrointestinal adverse effects with around 20% of patients experiencing some gastrointestinal adverse effect.[17] More serious adverse events, including fecal impaction, bowel obstruction, and ileus are reported in case reports of sevelamer therapy.[34] This may be attributed to the increase in size of the sevelamer tablets when hydrated in the gastrointestinal tract. Navaneethan et al completed a systematic review of 40

randomized controlled trials involving over 6,000 patients taking phosphate binders.[18] Overall the frequency of adverse events was comparable among the agents. The rate of gastrointestinal side effects was higher with sevelamer therapy and the rate of hypercalcemia was higher with calcium acetate therapy. The 2012 KDIGO Clinical Practice Guidelines recommend reducing or restricting the dose of calcium based phosphate binders, like calcium acetate, for patients on dialysis with persistent or recurrent hypercalcemia.[35] Sevelamer and lanthanum have not demonstrated an increase in serum calcium. Lanthanum is a trivalent cation and my exhibit similar toxicities to aluminum in CKD.[36] To date, accumulation of lanthanum in bones and tissues has not been reported and is unlikely because it is not systemically absorbed but long term data is not available.[14]

Table 2. Adverse Events Reported with the Phosphate Binding Agents[16-18]

	Calcium Acetate	Sevelamer	Lanthanum
Contraindications	Hypercalcemia Renal calculi	Bowel obstruction	None
Warnings/precautions	Mild to severe hypercalcemia may occur, especially if on concomitant vitamin D therapy Use with caution in patients at increased risk of cardiac arrhythmias	Use with caution in patients with gastrointestinal disorders including dysphagia, constipation, major gastrointestinal surgery, swallowing disorders, or severe gastrointestinal motility disorders May bind to some drugs and decrease their absorption May reduce absorption of vitamin D, E, K, or folic acid Tablets may be a choking hazard, especially if broken or crushed as they will rapidly expand in water/saliva	Use with caution in patients with active peptic ulcer disease, ulcerative colitis, Crohn's disease, or bowel obstruction as safety and efficacy has not been established in these populations
Adverse Events			
Abdominal pain	NR	9%	5%
Allergic skin reactions	NR	NR	rare
Bowel obstruction	NR	rare	rare
Constipation	NR	8%	rare
Diarrhea	>10%	19%	NR
Dizziness	rare	NR	NR
Dyspepsia	NR	16%	rare
Edema	rare	NR	NR
Fecal impaction	NR	rare	rare
Flatulence	NR	8%	NR
Hypercalcemia	>10%	5-7%	NR
Ileus	NR	rare	rare
Nausea	1-10%	20%	11%
Peritonitis	NR	8% (peritoneal dialysis)	NR
Pruritus	rare	rare	NR
Rash	NR	rare	NR

Vomiting	1-10%	22%	9%
Weakness	rare	NR	NR

Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive; NR = not reported

Summary

The phosphate binding agents are indicated in the reduction of hyperphosphatemia in end-stage renal disease. Current Kidney Disease Practice Guidelines (KDIGO, 2012) support the prevention of hyperphosphatemia with phosphate binders in patients with CKD but do not recommend one agent over another. Choice of agent should be based on individual patient characteristics, phosphate and calcium consumption, lab values, tolerability, and cost. This report evaluates the clinical efficacy and safety of calcium acetate, lanthanum, and sevelamer. The included agents were evaluated in eight clinical studies and one meta-analysis. Overall, sevelamer, lanthanum, and calcium acetate demonstrated similar rates of efficacy. One study reported a reduction in mortality with sevelamer in those over the age of 65. The most common adverse effect reported with the agents is gastrointestinal upset including nausea, vomiting, and diarrhea. In clinical trials, hypercalcemia was reported more frequently in patients taking calcium acetate and gastrointestinal upset was reported more frequently in patients taking sevelamer. Current clinical practice guidelines recommend reducing or restricting the dose of calcium based phosphate binders, like calcium acetate, in patients with persistent hypercalcemia. Overall, the phosphate binding agents are safe and efficacious in the reduction and prevention of hyperphosphatemia in patients with CKD.

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Evidence Tables

Reference/Study Design	N	Patient Population	Treatment Interventions	Results	Adverse Effects
Navaneethan et al, 2011[25] Cochrane Review	7,631	Patients with CKD stages 3-5D	lanthanum carbonate sevelamer hydrochloride calcium-based binders	sevelamer = lanthanum = calcium-based	sevelamer = more GI effects calcium-based = more hypercalcemia
Block et al, 2012[26] Randomized, double-blind, parallel study	148	Patients with CKD and normal phosphorous levels	lanthanum carbonate sevelamer carbonate calcium acetate	lanthanum > sevelamer = calcium-based > placebo	All increased calcifications
Kasai et al, 2012[27] Randomized, open-label, crossover study	42	Patients 18+ with CKD on HD for at least 3 months	lanthanum carbonate sevelamer hydrochloride	lanthanum = sevelamer	sevelamer > lanthanum
Gulati et al, 2010[28] Randomized, open-label, parallel study	19	Patients 2-18 with CKD stages 3 & 4	sevelamer hydrochloride calcium acetate	sevelamer = calcium acetate	sevelamer = calcium acetate
Wilson et al, 2009[29] Randomized, comparative safety study	1,354	Patients on dialysis	lanthanum carbonate "standard therapy"	lanthanum = "standard therapy"	lanthanum = "standard therapy"
St. Peter et al, 2008[30] Secondary analysis using CMS data	1,947	Patients 18+ on HD for at least 3 months	sevelamer hydrochloride calcium-based binders	<u>Mortality and Hospitalizations</u> sevelamer = calcium-based	<u>Pt. discontinued</u> sevelamer > calcium-based <u>Investigator discontinued</u> calcium-based > sevelamer

Delmez et al, 2007[31] Randomized, double-blind, crossover study	79	Patients receiving hemodialysis	sevelamer carbonate sevelamer hydrochloride	sevelamer carbonate = sevelamer hydrochloride	sevelamer hydrochloride> sevelamer carbonate
Suki et al, 2007[32] Multicenter, randomized, open-label, parallel study	1,068	Patients 18+ on HD for at least 3 months	sevelamer hydrochloride calcium-based binders	<u>Patients over 65 mortality</u> sevelamer > calcium-based <u>All patients ages mortality</u> sevelamer = calcium-based	sevelamer > calcium-based
Qunibi et al, 2004[33] (CARE) Multicenter, randomized, double-blind study	100	Adults on HD for ≥ 3 mo, stable dose of phosphate binder and IV vit. D > 1 mo, phosphate levels > 6 after 1-3 week of no binder	calcium acetate sevelamer hydrochloride	calcium acetate > sevelamer hydrochloride	calcium acetate = sevelamer hydrochloride

Key: HD = hemodialysis; CMS = Centers for Medicare and Medicaid Services; IV = intravenous