Phosphate Binders Review

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Phosphate Binders Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
calcium acetate (PhosLo®)	generic	Control of hyperphosphatemia in end stage renal disease (ESRD) patients
calcium acetate (Eliphos™)	Hawthorn Pharmaceuticals	Control of hyperphosphatemia in end stage renal disease (ESRD) patients
lanthanum carbonate (Fosrenol®)	Shire US	Reduce serum phosphate in patients with ESRD
sevelamer hydrochloride (Renagel®)*	Genzyme	Control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis
sevelamer carbonate (Renvela™)	Genzyme	Control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis

*Sevelamer hydrochloride (Renagel) is scheduled to be removed from the United States' market by September 30, 2009.[1]

Overview

Chronic kidney disease (CKD) affects approximately 26 million Americans in the United States.[2] One complication of CKD is hyperphosphatemia. As kidney function declines, the ability to eliminate phosphorus declines, which results in hyperphosphatemia. Elevated levels of phosphorus inhibit the conversion of 24-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol). The reduction in calcitriol decreases intestinal absorption of calcium and eventually leads to hypocalcemia. In end stage renal disease (ESRD), patients are at risk for several complications of hyperphosphatemia including the development of renal bone disease, extraosseous calcifications of soft tissue and vasculature. Hyperphosphatemia (> 6.5 mg/dL) is also associated with increased risk of death.[3,4,5,6]

Direct stimulators of parathyroid hormone (PTH) secretion include hypocalcemia, low levels of calcitriol, and hyperphosphatemia. Secondary hyperparathyroidism contributes to abnormal bone metabolism observed in CKD. Management of renal osteodystrophy includes maintenance of calcium and phosphate balance, vitamin D supplementation, reducing patient exposure to aluminum, and in some cases, parathyroidectomy.

Another complication of hyperphosphatemia is extraosseous calcifications of soft tissue and vasculature. Soft tissue calcifications can occur in vascular and cardiac tissue leading to increased morbidity and mortality.[7,8] The calcium x phosphorus (Ca X P) product is calculated by using the patient's corrected serum calcium level and serum phosphorus level; the desired product level is less than 55 mg^2/dL^2. Patients with elevated Ca X P product values are at significantly higher risk of death.[9]

The National Kidney Foundation has released guidelines in 2003 regarding the management of hyperphosphatemia and bone-related disorders in patients with renal impairment. According to

the National Kidney Foundation – Kidney Disease Quality Outcome Initiative (NKF-K/DQOI™), patients with CKD on dialysis should have serum phosphorus level maintained between 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L).[10] Treatment of hyperphosphatemia includes the reduction of dietary phosphorus, phosphate binding therapy, and removal of phosphorus by dialysis.[11] Dietary phosphorus should be limited when serum phosphorus exceeds 5.5 mg/dL (1.78 mmol/L) in dialysis patients.

Pharmacology

Phosphate-binding agents decrease phosphorus absorption from the gastrointestinal (GI) tract by binding dietary phosphorus. Aluminum salts were once used to bind phosphate due to the excellent binding potency of aluminum; however, aluminum absorption lead to aluminum accumulation and toxicity.

Calcium-containing salts not only maintain positive calcium balance but also bind phosphorus. Calcium and vitamin D analog supplementation may be necessary to slow or prevent renal bone disease. Calcium acetate (PhosLo, Eliphos) is one of the most commonly used calcium salts. In the event of hypocalcemia, calcium supplementation and/or vitamin D sterols should be administered.

Calcium-based phosphate binders should not be used when hypercalcemia is present [corrected calcium greater than 10.2 mg/dL (2.54 mmol/L)] or when plasma PTH levels are less than 150 pg/mL (16.5 pmol/L) on two consecutive measurements.

Three non-calcium based phosphate binders are now available and offer an alternative to calcium-based agents when hypercalcemia is present. Sevelamer (Renagel, Renvela) is a non-calcium, non-aluminum, non-magnesium, non-absorbable hydrogel that binds phosphorus. Sevelamer is available in two salt forms – sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela). Another phosphate-binding agent is lanthanum carbonate (Fosrenol). Lanthanum is a naturally occurring earth element with a high affinity for phosphorus. Lanthanum binds with phosphorus to form insoluble lanthanum phosphate.

Pharmacokinetics

Absorption rate of calcium is dependent on numerous factors including the presence of vitamin D. Bioavailability of calcium acetate is 30 to 40 percent.[12,13]

Sevelamer is not absorbed and is excreted in the feces. Sevelamer also reduces low-density lipoprotein (LDL-C) and total cholesterol.[14,15]

Lanthanum carbonate has an extremely low bioavailability (0.002 percent) and is primarily excreted in the feces.[16,17] Lanthanum carbonate dissociates in the upper GI tract to release lanthanum ions that bind phosphate from food. Lanthanum forms insoluble complexes with phosphate that are eliminated via the feces.

Contraindications/Warnings

Calcium acetate (Phoslo, Eliphos) should not be administered in the presence of hypercalcemia.[18,19]

Sevelamer is contraindicated in the presence of hypophosphatemia or bowel obstruction.[20,21] Safety and efficacy of sevelamer in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been

established. Caution should be exercised when sevelamer is used in patients with these GI disorders.

Lanthanum has no known contraindications.[22] Abdominal x-rays of patients taking lanthanum may have a radio-opaque appearance typical of an imaging agent. Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in lanthanum clinical studies. Caution should be used in patients with these conditions.

Drug Interactions

Very limited drug interaction studies were performed with the agents. Calcium acetate may reduce the bioavailability of tetracyclines.[23,24]

Sevelamer does not interact with digoxin, warfarin, enalapril, metoprolol, or ferrous sulfate.[25,26,27,28] Concurrent administration of sevelamer and ciprofloxacin has been shown to reduce bioavailability of ciprofloxacin in single dose studies.[29,30,31]

Lanthanum was studied with digoxin, warfarin, and metoprolol in a single-dose healthy volunteer study.[32] No interaction was noted in the single dose study. In a single dose study of ciprofloxacin and lanthanum, a reduction of more than 50 percent of the absorption of ciprofloxacin was observed with concurrent administration.[33] Lanthanum does not interact with the CYP450 enzyme system. As a precaution, drugs which interact with antacids should be administered at least two hours before or after lanthanum.

Adverse Effects

Drug	Hypercalcemia	Diarrhea	Constipation	Nausea	Vomiting
calcium acetate (PhosLo)[34]	reported	nr	reported	reported	reported
calcium acetate (Eliphos)[35]	reported	nr	reported	reported	reported
lanthanum carbonate (Fosrenol)[36] n=533	0	13	6	16	18
calcium carbonate n=267	20	10	7	13	11
sevelamer hydrochloride (Renagel)[37] n=99	nr	19	8	20	22
sevelamer carbonate (Renvela)[38]	nr	19	8	20	22

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Detection of valvular and vascular calcifications by electron beam tomography (EBT) in CKD patients is a current focus of research. Calcifications are frequently observed in CKD patients and indicate an unfavorable prognosis. Numerous trials have sought to compare the phosphate binders and measure the impact of each agent on the progression of the vascular and/or valvular calcifications.[39,40,41,42,43,44,45,46,47,48,49] Most of the trials have been performed in small patient populations in open-label trials.

Calcium acetate can cause hypercalcemia; therefore, monitoring of serum calcium is suggested. Symptoms of mild hypercalcemia (serum calcium greater than 10.5 mg/dL) may include constipation, anorexia, nausea and vomiting. Severe hypercalcemia (serum calcium greater than 12.5 mg/dL) may present as confusion, delirium, stupor, and coma. A reduction in calcium supplementation and dialysis will help reduce calcium levels.[50]

Lanthanum deposits into bone over a period of several years. Long-term effects of lanthanum in bone are not known.[51] There have been no differences in the rates of fracture or mortality in patients treated with lanthanum compare to alternative therapy for up to three years.[52]

In a one-year study with 20 patients, lanthanum was shown to be deposited into bone in low concentrations.[53] After discontinuing lanthanum for two years, plasma and bone concentrations of lanthanum were still detectable although at lower concentrations than during active treatment. Bone biopsies from 105 patients treated for up to 4.5 years showed rising lanthanum levels. Estimated elimination half-life from bone ranged from 2 to 3.6 years.[54] A total of 22 patients have received lanthanum as a part of a clinical to monitor the efficacy and safety.[55] Lanthanum doses were 2,250 to 3,000 mg per day for two-thirds of the patients. Efficacy in reducing serum phosphate and Ca X P product were maintained up to six years. No new adverse effects were reported; no increase in the incidence of adverse events were reported. No evidence of adverse effects on the liver, bone or the central nervous system was observed.

Special Populations

Pediatrics

Safety and efficacy data for pediatric use of agents in this class have not been established. NKF-KDOQI guidelines for bone and mineral metabolism in pediatric patients on dialysis currently suggest calcium based phosphate binders (Evidence rating) especially in infants and young children. In older children and adolescents, either sevelamer, or calcium-based phosphate binders may be used (Opinion rating).[56] European guidelines for prevention and treatment of renal osteodystrophy in children with CKD recommend calcium-based phosphate binders as first line therapy.[57] Sevelamer is suggested as an alternative therapy. Long-term effects on bone and safety profile of lanthanum in children are not yet available. Due to bone deposition and uncertain long-term effects on bone, lanthanum is not recommended in pediatric patients.[58]

A randomized, open-label study with 18 children (ages < 1 to 18 years) with renal insufficiency or CKD undergoing dialysis found that sevelamer and calcium acetate provided similar phosphorus control over eight weeks.[59] Patients underwent a two-week washout period then underwent treatment for eight weeks with either agent in a cross-over fashion. Doses were titrated as needed to achieve target levels of phosphorus. No difference in phosphorus levels between the two treatments were observed at eight weeks. In the crossover study, hypercalcemia occurred more frequently with calcium acetate ($p<0.0005$) whereas metabolic acidosis was more common with sevelamer ($p<0.005$). Total cholesterol (-27 percent) and LDL-C (-34 percent) were decreased significantly with sevelamer ($p<0.02$, $p<0.005$).

A total of 29 pediatric patients receiving peritoneal dialysis with bone biopsy-proven secondary hyperparathyroidism were randomized to calcium carbonate or sevelamer.[60] Patients could also receive oral calcitriol or doxercalciferol for eight months. Serum phosphate levels were 5.5 and 5.6 mg/dL in calcium- and sevelamer-treated patients, respectively. Serum calcium levels and Ca X P product were increased in the calcium group. Hypercalcemia (>10.2 mg/dL) was reported more frequently with calcium ($p<0.01$). PTH levels decreased significantly from baseline (both $p<0.01$) with no between-group differences following treatment. Bone biopsies performed after eight months demonstrated improvement in skeletal lesions in patients from both treatment groups, and bone formation rates were within normal limits in 75 percent of patients.

Pregnancy

All agents in this class are Pregnancy Category C.[61,62,63,64,65]

Dosages

Drug	Initial Dosing	Maintenance Dosing	Availability
calcium acetate (PhosLo)	1,334 mg with each meal 2 tablets per meal	2,001 - 2,668 mg with each meal 3-4 tablets per meal	667 mg gelcap
calcium acetate (Eliphos)	1,334 mg with each meal 2 tablets per meal	2,001 - 2,668 mg with each meal 3-4 tablets per meal	667 mg tablet
lanthanum carbonate (Fosrenol)	1,500 mg with each meal 2 tablets per meal Tablets should be chewed completely	1,500 - 3,000 mg in divided doses daily given with meals 1-2 tablets per meal Tablets should be chewed completely	500, 750, 1,000 mg chewable tablets
sevelamer hydrochloride (Renagel)	400 - 1,600 mg with each meal	800 - 1,600 mg with each meal	400, 800 mg tablets
sevelamer carbonate (Renvela)	800 – 1,600 mg with each meal 1-2 tablets per meal	1,600 – 2,400 mg with each meal 2-3 tablets per meal	800 mg tablets

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included

for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

calcium acetate (PhosLo) and sevelamer (Renagel)

In an open-label, randomized trial, calcium acetate and sevelamer were compared for safety and efficacy in controlling hyperphosphatemia in hemodialysis patients.[66] Following a two-week washout period, 84 patients were randomized to calcium acetate or sevelamer for eight weeks. Patients were then crossed over to the alternate therapy following an additional two-week washout period. Doses of both agents were titrated to achieve appropriate phosphate levels. A similar decrease in phosphate levels was observed between the two therapies (sevelamer -2.0±2.3mg/dL versus calcium acetate -2.1±1.9 mg/dL). Hypercalcemia (serum calcium >11 mg/dL) was observed in 22 percent of patients receiving calcium acetate. Five percent of patients receiving sevelamer developed serum calcium > 11 mg/dL (versus calcium acetate; $p<0.01$), and the incidence was not different from the incidence of hypercalcemia during the washout period. A mean reduction of LDL-C of 24 percent was observed with sevelamer treatment.

The CARE study was an evaluation of calcium acetate and sevelamer to see which therapy achieved the treatment goals of phosphorus (≤ 5.5 mg/dL) and the Ca X P product (≤ 55 mg^2/dL^2).[67] One hundred hemodialysis patients were randomized in the double-blind, eight-week trial. Patients treated with calcium acetate achieved lower serum phosphorus (difference of -1.08 mg/dL, $p=0.0006$), higher serum calcium (difference of +0.63mg/dL, $p<0.0001$), and lower Ca X P product (difference of -6.1 mg^2/dL^2) than the sevelamer-treated patients based on time-averaged concentrations for weeks one to eight. For each week, calcium acetate-treated patients were 20 to 24 percent more likely to be at goal for phosphate levels and 15 to 20 percent more likely to be at goal for the Ca X P product. Hypercalcemia was more common with calcium acetate (OR 6.1, 95% confidence interval [CI], 2.8-13.3, $p<0.0001$). At week eight, intact PTH levels were not significantly different.

sevelamer (Renagel) and calcium therapy

An open-label study evaluated 55 hemodialysis patients to determine the effects of sevelamer with and without calcium supplementation on serum phosphorus, calcium and PTH.[68] Patients were randomized following a two-week washout period to sevelamer or sevelamer with 900 mg of elemental calcium daily on an empty stomach. Forty-nine percent of all patients were also taking vitamin D metabolites. Efficacy of treatment in reducing serum phosphorus was similar for both groups. An insignificant increase in serum calcium occurred in the sevelamer plus calcium group. Non-users of vitamin D metabolites randomized to sevelamer plus calcium had a significant decrease in PTH ($p=0.006$) compared to sevelamer therapy alone. The sevelamer plus calcium group showed decreasing PTH levels throughout the study. All therapies were well tolerated.

The Dialysis Clinical Outcomes Revisited (DCOR) study was an open-label, prospective, randomized, controlled, three-year trial comparing sevelamer and calcium-based phosphate binders (PhosLo or calcium carbonate) for all-cause mortality and cause-specific mortality (cardiovascular mortality, infect and other causes) in 2,103 patients.[69] Patients were followed for up to 45 months. Forty-three percent of patients enrolled were followed for more than two years, and 1,068 patients completed the study. Seventy percent of the calcium group took PhosLo tablets; the remaining 30 percent took calcium carbonate. The mean prescribed dose was 5.3 g calcium acetate, 4.9 g calcium carbonate and 6.9 g sevelamer. The primary endpoint was all-cause mortality, and no difference between the two groups was observed (relative risk 0.93, 95% CI, 0.79-1.1; p=0.4). An evaluation of patients who completed at least two years in the study (43 percent) revealed a difference in all-cause mortality favoring sevelamer (p=0.02). Deaths were reported in 26 (n=142) and 27 (n=147) percent of the sevelamer and calcium-based groups, respectively. Overall cardiovascular mortality (p=0.53) and infection (p=0.68) rates were similar between the two groups. When evaluating cardiovascular mortality and age (> 65 years or < 65 years), all-cause mortality and cardiovascular mortality were both significantly lower with sevelamer in the older population compared to the calcium group (both p=0.02). The time-weighted mean serum calcium values, total cholesterol and LDL-C values were significantly lower in the sevelamer group (all p<0.0001). The Ca X P product was similar in both groups (p=0.60).

As a secondary endpoint, hospitalization and cardiovascular morbidity were extracted from a merger of the DCOR study patient data and the Centers for Medicare and Medicaid Services (CMS) ESRD database.[70] Patients included in the analysis used Medicare as the primary payer for treatment. Outcome parameters and cardiovascular comorbidity assessments were derived from Medicare claims data. A greater percentage of calcium-treated patients had atherosclerotic heart disease. Sevelamer had a positive effect on hospitalization days (p=0.009) and the multiple hospitalization rates (p=0.046) compared to the calcium-based binder group. No significant effect was seen in all-cause hospitalization rate or cardiovascular morbidity over the study time frame. Early discontinuation was similar in both groups (sevelamer n=502; calcium n=533; p=0.15). The lead author disclosed support from the manufacturer of sevelamer.

sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela)

In a double-blind, randomized, cross-over trial, sevelamer carbonate and sevelamer hydrochloride were compared in 79 hemodialysis patients for effects on serum phosphorus, lipids, and bicarbonate levels.[71] Patients received eight weeks of treatment followed by eight weeks of the alternative treatment. The mean serum phosphorus was 4.6+/-0.9 and 4.7+/-0.9 mg/dL during sevelamer carbonate and sevelamer hydrochloride treatment, respectively. Mean total cholesterol and LDL-C were 144 and 59.5 mg/dL, respectively, during sevelamer carbonate treatment and 139 and 56 mg/dl, respectively, during sevelamer hydrochloride treatment. Serum bicarbonate levels increased by 1.3 mEq/L during sevelamer carbonate treatment. Fewer gastrointestinal adverse events were observed with sevelamer carbonate.

lanthanum (Fosrenol) and calcium carbonate

In a phase III, open-label study, lanthanum and calcium carbonate were compared for the effects on renal osteodystrophy in 98 dialysis patients.[72] Patients were randomized to lanthanum or calcium carbonate following a baseline bone biopsy. Bone biopsies were also evaluated after one year. Periodic assessments of electrolytes and adverse effects were recorded. At one year, 63 sets of bone biopsies were available. Serum phosphate was well

controlled in both groups. Hypercalcemia was reported less often with lanthanum than calcium carbonate (six and 49 percent, respectively). Subtypes of renal osteodystrophy at baseline were similar in both groups with the mixed type being most common. Percent of patients with adynamic bone, osteomalacia, or hyperparathyroidism was reduced by lanthanum therapy from 36 to 18 percent over one year. The calcium group saw an increase from 43 percent to 53 percent of patients with evidence of adynamic bone, osteomalacia, or hyperparathyroidism after one year. No aluminum-type effects on bone were seen with lanthanum use. Adverse effects were mostly GI in nature. Both groups had similar discontinuation rates.

A randomized, open-label trial compared lanthanum and calcium carbonate for control of serum phosphate levels over 20 weeks.[73] Patients (n=800) underwent a washout period and then were randomized to lanthanum or calcium carbonate. Patients completed a five-week dose titration period. Control of phosphate levels (≤5.58 mg/dL) was achieved by 65.8 and 63.9 percent of lanthanum- and calcium-treated patients, respectively, during 20 weeks of active treatment. Hypercalcemia was reported in 20.2 percent of calcium-treated patients compared to 0.4 percent of patients receiving lanthanum. The Ca X P product was slightly better controlled with lanthanum. The most common daily dose of lanthanum was 1,500 mg with a range of 375 to 3,000 mg per day. The most frequently used calcium carbonate daily dose was 3,000 mg (1,200 mg elemental calcium) with a range of 1,500 to 9,000 mg per day.

The above evaluation by Hutchinson and colleagues was extended an additional six months and then two years.[74] Patients on lanthanum continued the maintenance dose as established in the previous study. Patients originally assigned to the calcium group were switched to lanthanum and underwent dose titration over five weeks. A total of 518 patients entered the six-month extension. Mean serum phosphorus throughout the six-month study extension was 5.5 mg/dL and 5.7 mg/dL in the lanthanum group and the group that switched from calcium to lanthanum, respectively. Hypercalcemia was reported in 2.7 percent of patients. A total of 161 patients entered the two-year extension phase; patients underwent a dose titration to achieve acceptable phosphorus control. Ninety patients completed the two years, and 46 of the patients were from the original lanthanum group. At the end of two years, 59 percent of the 90 remaining patients had serum phosphorus levels ≤ 5.6 mg/dL. The most common adverse events were GI related.

Summary

Control of hyperphosphatemia is critical to the prevention and delay of renal osteodystrophy and soft tissue calcifications. Hyperphosphatemia is an independent risk factor associated with increased all-cause mortality. Opportunities for improvement in the management of hyperphosphatemia were described in the Dialysis Outcomes and Practice Patterns Study (DOPPS) where eight percent of patients exhibited phosphate levels below the target range and 52 percent of patients had phosphate levels exceeding the target range.

Phosphate-binding therapy with calcium acetate (PhosLo, Eliphos) is as effective as sevelamer (Renagel, Renvela) in reducing serum phosphate levels. Hypercalcemia occurs more frequently with calcium acetate (PhosLo, Eliphos) in a small portion of patients. Calcium supplementation may be required with sevelamer (Renagel, Renvela) to enhance control of secondary hyperparathyroidism.

Sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela) have been compared in one trial which demonstrated similar efficacy. Increased serum bicarbonate levels were observed in the serum carbonate (Renvela) group compared to the sevelamer hydrochloride group (Renagel). The manufacturer is withdrawing Renagel from the US market by the end of

September 2009.

Lanthanum (Fosrenol) is another non-calcium, non-aluminum, phosphate-binding agent. The long-term effects of lanthanum (Fosrenol) on bone remain unclear. Sevelamer and lanthanum have not been directly compared in the published literature. All phosphate binders are efficacious in reducing serum phosphate levels.

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