Phosphate Binders Used in Chronic Kidney Disease
September 2010

INTRODUCTION:[1-6]

Chronic Kidney Disease (CKD) is a multi-factorial condition affecting approximately 26 million American adults. CKD is most frequently caused by: diabetes, hypertension, autoimmune disease, systemic infections, urinary tract infections, urinary stones, urinary tract obstruction, neoplasm, family history, recovery from acute kidney failure, reduced kidney mass, medications and low birth rate. Of note, diabetes and hypertension are conditions frequently encountered in the American Indian/Alaska Native population. Approximately 16.3% of American Indian/Alaska Natives adults have diagnosed diabetes and have a 3.5 times higher rate of diabetes-related kidney failure compared with the general US population.

CKD is generally a progressive and irreversible condition that can eventually lead to "deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones."[1] At CKD stage 3 (see table 1), the kidneys ability to excrete phosphorus becomes reduced, leading to hyperphosphatemia and elevated parathyroid hormone (PTH). Additionally, 1, 25-hydroxyvitamin D (1, 25 $(OH)_2D$) is reduced, thereby reducing intestinal calcium absorption. Therefore, one of the focal points of therapy is correction of the associated hyperphosphatemia. This hyperphosphatemia has been noted to increase mortality in patients with CKD. The associated effects of CKD on mineral metabolism has notable effects on soft tissue calcification, including areas of the lung (pulmonary fibrosis, hypertension) and heart (right side ventricular hypertrophy, right side heart failure, valvular calcification, arrhythmia's, coronary artery calcification) among others. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines use the term 'CKD-Mineral and Bone Disorder (CKD-MBD)' to describe the abnormalities that are secondary to CKD.

This monograph will focus on correcting hyperphosphatemia with the non-calcium containing phosphate binders, but information on the calcium containing phosphate binder, calcium acetate, will be included for some comparisons and discussion of place in therapy.

Table 1. Stages of Chronic Kidney Disease[2]

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney Failure	< 15 (or dialysis)

KEY QUESTIONS:

1. How do the calcium and non-calcium containing phosphate binders compare in effectiveness clinically in the treatment of CKD related hyperphosphatemia?

2. How do the calcium and non-calcium containing phosphate binders compare in terms of safety/tolerability in patients with hyperphosphatemia?

3. How should the calcium and non-calcium containing phosphate binders be best utilized in the treatment of hyperphosphatemia?

PHARMACOLOGY/PHARMACOKINETICS: [7-10]

Calcium acetate (PhosLo®) is a calcium based phosphate binder that combines with dietary phosphate to form insoluble calcium phosphate, which is excreted in the feces.

Sevelamer carbonate and Sevelamer hydrochloride (Renvela®/ Renagel®) are non-absorbed polymers that binds phosphate molecules in the gastrointestinal tract. This absorption thereby decreases the amount of phosphate absorbed into systemic circulation, thus lowering serum phosphorus concentration.

Lanthanum carbonate (Fosrenol®) is a non-calcium, non-aluminum agent that dissociates in the acidic environment of the upper gastrointestinal tract. Upon dissociation, lanthanum ions are released to bind dietary phosphate. This binding inhibits absorption by forming insoluble complexes of lanthanum phosphate thereby decreasing serum phosphate and calcium phosphate product.

Table 2. Pharmacokinetic Properties of phosphate binders

Drug	Absorption	Distribution	Metabolism	Excretion
Calcium acetate	Sysemically absorbed: Fasting-40% Non-fasting-30%			Primarily Feces and urine
Sevelamer (carbonate and hydrochloride)	Not absorbed			
Lanthanum carbonate	Oral: <0.002% Food: not studied	Protein binding: >99%	Not metabolized T1/2: plasma, 53 hours; bone, 2-3.6 years	Primarily feces, urine <2%

FDA APPROVED INDICATIONS:[7-9]

Calcium acetate (PhosLo®) is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

Sevelamer carbonate (Renvela®) is indicated for the control of serum phosphorus in patients with CKD on dialysis.

Sevelamer hydrochloride (Renagel®) is indicated for the control of serum phosphorus in patients with CKD on dialysis. The safety and efficacy of Renagel in CKD patients who are not on dialysis have not been studied.

Lanthanum carbonate (Fosrenol®) is indicated for the reduction of serum phosphate in patients with end stage renal disease.

CURRENT NATIONAL CORE FORMULARY ALTERNATIVES:[11]

Currently, no non-calcium containing phosphate binder is available on the IHS National Core Formulary (NCF). Calcium (any product) is currently available on the NCF.

DOSAGE AND ADMINISTRATION:[7-9]

Table 3. Dosing and administration

Drug	Serum Phosphorus	Usual Dose	Hepatic Dysfunction
Calcium acetate (PhosLo®)		2 capsules with each meal; may be increased gradually to attain serum phosphate <6mg/dL, as long as hypercalcemia does not develop	None
Sevelamer carbonate (Renvela®)	>5.5 - <7.5mg/dL ≥ 7.5mg/dL	Tablets: 1 tablet tid with meals Powder: 0.8g tid with meals 2 tablets tid with meals 1.6g tid with meals	None
Sevelamer hydrochloride (Renagel®)	>5.5 - <7.5mg/dL ≥ 7.5 - <9 mg/dL ≥9mg/dL	800mg tid with meals 1600mg tid with meals 1600mg tid with meals	None
Lanthanum carbonate (Fosrenol®)		Initial dose: 1500mg/day (divided doses taken with meals) Max:	None

		3750mg/day Titration: titrate in increments of 750mg/day every 2-3 weeks until serum phosphate acceptible	

GUIDELINES/SYSTEMATIC REVIEWS:

Indian Health Diabetes Best Practice: Chronic Kidney Disease:[6]

In 2009, the Division of Diabetes Treatment and Prevention (DDTP) revised their best practice document for CKD. They raised 5 key recommendations for managing patients with CKD.

- Identify patients at risk for CKD in order to prevent or prolong the development of end-stage kidney disease.
- Provide kidney disease education to the community to increase awareness of kidney protective measures and reduce end-stage kidney disease rates.
- Control blood pressure.
- Include a registered dietician and a pharmacist on the multi-disciplinary care team.
- Develop clear mechanisms to facilitate vascular access placement, transplant referral, and diagnostic imaging.

These guidelines were primarily focused on programmatic changes and recommendations to create a program for successful management of CKD. One systematic recommendation was the use of "evidence-based practice guidelines and protocols to facilitate clinical decision-making and improve diabetes outcomes" including laboratory measurement recommendations (GFR estimates, urine albumin-to-creatinine ratio, hemoglobin level, albumin, lipids, bicarbonate, calcium, phosphorus and alkaline phosphatase. This document does not specifically address the treatment options for CKD related hyperphosphatemia.

KDIGO:[1]

The 2009 KDIGO clinical practice guidelines addressed the diagnosis, evaluation, prevention and treatment of CKD-MBD. These guidelines recommend appropriate dietary modifications such as reducing dietary phosphate intake in addition to treatment with phosphate-binding medications. The goal for CKD stage 3-5 patients is maintenance of serum phosphorus and calcium in the normal range. For patients with CKD stage 3-5, phosphate binding agents should be used to treat hyperphosphatemia with the choice being made based upon CKD stage, other CKD-MBD components, concomitant therapies and side-effect profile of the various agents. If hypercalcemia is present, they recommend restricting the calcium-containing phosphate binder dose and/or the calcitriol/vitamin D analog dose. This review stated that "all medications currently used as phosphate binders (calcium salts, aluminum salts, magnesium salts, sevelamer HCL and lanthanum carbonate) are effective in lowering serum phosphorus levels." It also found "insufficient comparative efficacy data on clinical outcomes to make a recommendation for the use of a specific binder for all patients." KDIGO also stated that evidence was not conclusive and that more research is needed" when discussing the role of calcium containing versus non-calcium containing phosphate binders and their effect on vascular calcification.

The use of calcium carbonate versus calcium acetate was discussed and it was noted that both are associated with hypercalcemia and GI side effects, but the KDOQI guidelines (discussed below) stated less hypercalcemia with the acetate salt.

Systematic search was conducted for head-to-head comparison of non-calcium containing phosphate binders to calcium based phosphate binders. This review yielded the following selected statements:

- Mortality data comparing sevelamer HCL and calcium based phosphate binders were inconsistent
- Sevelamer HCL slows arterial calcification in CKD 3-5 and 5D in some studies, but not all. Systematic data with other phosphate binders and their effect on vascular calcification had not been studied.
- "Clinical trials comparing calcium carbonate with lanthanum carbonate or sevelamer HCL do not show major differences among treatments" with regards to bone histology.
- Use of calcium based phosphate binders has lead to higher incidence of hypercalcemia and lower PTH levels as compared to sevelamer or lanthanum based regimens.

K/DOQI:[2]

The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines of 2003 discuss various facets of treatment associated with patients with CKD. This guideline established the frequently utilized stages of CKD (see table 1). As such, K/DOQI recommendations are frequently tied with these CKD stages.

The K/DOQI guidelines recommend the use of dietary phosphorus restrictions as a first-line step in controlling serum phosphorus levels. In CKD stage 3 or 4 patients whose phosphorus levels cannot be maintained with dietary restrictions, the use of phosphate binders is recommended. Expert opinion suggests that calcium-based phosphate binders be used as the initial therapy. It is noted that in CKD stage 5, calcium-based and non-calcium based phosphate binders are effective and may be used as primary therapy. There was a strong recommendation against the use of calcium-containing phosphate binders in patients with hypercalcemia or have elevated PTH levels on 2 consecutive visits. It was also recommend to use non-calcium-based phosphate binders preferentially for "dialysis patients with severe vascular and/or other soft tissue calcifications."

Navaneethan et al.[12]

In 2009, Navaneethan and colleagues published a systematic review of the evidence associated with the benefits and harms of phosphate binders in CKD. This review focused on randomized controlled trials of phosphate binders and focused on the following outcomes: Serum phosphorus, calcium and PTH, hypercalcemia, all-cause mortality and adverse effects. The authors identified 40 trials that included over 6400 patients. Its findings were:

- No significant RR of all-cause mortality between calcium carbonate and calcium acetate
- No significant RR of all-cause mortality between sevelamer versus calcium salts (RR 0.73;95% CI, 0.46-1.16)

- No significant difference in hypercalcemia risk between calcium acetate versus calcium carbonate
- A significant reduction in hypercalcemia was seen with sevelamer versus calcium salts (RR 0.47; 95% CI, 0.36-0.62)
- A significant reduction in hypercalcemia was seen with lanthanum versus calcium carbonate (RR 0.08; 95% CI, 0.02-0.32)
- No significant difference in GI adverse effects when comparing calcium acetate versus calcium carbonate
- No significant difference in GI adverse effects when comparing lanthanum carbonate to placebo or calcium carbonate
- Sevelamer had a significant increase in risk of GI adverse effects compared to calcium salts (RR 1.39; 95% CI, 1.04-1.87)
- No significant difference was seen when comparing serum phosphorus levels with calcium acetate versus carbonate
- No significant difference was seen when comparing serum phosphorus levels with lanthanum carbonate versus calcium carbonate
- A significant improvement in serum phosphorus was seen with sevelamer versus calcium salts (weighted mean difference (WMD) 0.21mg/dL; 95% CI 0.01 to 0.41)
- No significant difference in end-of-treatment calcium was see with calcium acetate versus carbonate
- A significant reduction in end-of-treatment calcium level was seen with sevelamer versus calcium salts (WMD -0.35 mg/dL; 95% CI -0.46 to -0.24)
- A significant reduction in end-of-treatment calcium level was seen with lanthanum carbonate versus calcium carbonate (WMD, -0.45 mg/dL; 95% CI -0.64 to -0.26)

Their finding was that "there are insufficient data to establish the comparative superiority of non-calcium-binding agents over calcium containing phosphate binders for such important patient-level outcomes as all-cause mortality and cardiovascular end points" and that additional trials are needed.

Jamal et al.[13]

A meta-analysis by Jamal and colleagues was published in 2009 and compared the effects on mortality of calcium-based and non-calcium-based phosphate binders in CKD. They focused on 8 randomized clinical trials. No significant differences were seen with respect to all-cause mortality between the two groups (RR 0.68; 95% CI 0.41-1.11). Data from cardiovascular events were non-significant also (RR 0.85; 95% CI 0.35-2.03), but were based on the results of two studies. Coronary artery calcification data (5 trials included) also revealed non-significant findings between groups.

Sprague[14]

A comparative review article was written by Sprague in 2007. This review compared the available calcium and non-calcium containing phosphate binders for efficacy, safety, compliance or pharmacoeconomics. His finding was that each of these classes are effective at reducing serum phosphorus. This article suggested that lanthanum may reduce pill burden for patients,

but it must be mentioned that it utilized the sevelamer HCL dosage form. It listed calcium salts as the "gold standard," but issues with calcium load must be considered.

EFFICACY:

Sevelamer:
Fan et al.[15] published the results of an open-label, randomized, crossover design study of patients who were actively on hemodialysis. It included 31 patients who were randomly assigned to receive sevelamer carbonate powder (Renvela®) or sevelamer HCL (Renagel®) for 4 weeks, then patients received 4 weeks of the other regimen. This study was designed to compare the safety and efficacy of sevelamer powder versus sevelamer HCL tablets in patients on hemodialysis. The results showed that sevelamer carbonate and sevelamer HCL were equivalent in their effect on serum phosphorus and well tolerated.

A study by Ketteler et al.[16] looked at the efficacy and tolerability of sevelamer carbonate in patients with CKD and hyperphosphatemia. It was an open-label, dosage-titration designed trial of patients with elevated phosphorus level ($\geq$ 5.5mg/dL) with primary outcome being change from baseline serum phosphorus and secondary outcomes of percentage of serum phosphorus responders, change in lipids, calcium-phosphorus product, bicarbonate and safety/tolerability. There were statistically significant reductions in:

- Mean serum phosphorus levels
- Serum calcium-phosphorus product
- Total and LDL cholesterol

A significant increase in serum bicarbonate level was also seen in this study. Sevelamer carbonate was well tolerated in this study with minor to moderate GI disturbance being the most frequently reported. Of note, this study was in non-dialysis patients (non-FDA indicated) and sevelamer is most frequently utilized in patients on dialysis.

St. Peter and colleagues published a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) trial.[17] Patients in DCOR had received sevelamer or calcium-based phosphate binders. This analysis focused on Centers for Medicare & Medicaid Services (CMS) data to compare study drugs effect on mortality, morbidity and hospitalization. Of note, all patients from DCOR were on hemodialysis for at least 3 months. All-cause mortality was not statistically different between the sevelamer and calcium-based group (unadjusted RR 1.02; 95% CI 0.89-1.17; p=0.8). Morbidity data (i.e. cardiovascular, vascular access, fracture, infection) showed a trend in favor of sevelamer, but lacked statistical significance. A statistically significant difference in favor of sevelamer was seen with hospitalizations (unadjusted RR, 0.90; 95% CI 0.82-0.99; p=0.03).

A study by Suki et al. also looked at the effect of sevelamer versus calcium-based phosphate binders on mortality (all-cause and cause-specific).[18] This trial was a randomized, open-label, parallel design in over 2100 hemodialysis patients. No difference was seen between study groups with respect to all-cause and cause-specific mortality (hazard ratio=0.93; 95% CI 0.79-1.10). A sub-group analysis found an age related difference in mortality for patients $\geq$ 65 years old (sevelamer 18.2 per 100 patient-years; calcium 23.4 per 100 patient-years; p=0.02).

Slatopolsky and colleagues published an article published the results of an open-label, dose-titration study to determine the safety and efficacy of sevelamer HCL.[19] The primary objective was the effect of sevelamer HCL on lowering serum phosphorus and safety in patients on hemodialysis. The secondary objectives were serum PTH and lipid profiles. After 8 weeks of sevelamer HCL, serum phosphorus was reduced to 6.6 $\pm$ 1.9 mg/dL (baseline after wash-out, 9.1 $\pm$2.4mg/dL; p<0.0001). A beneficial effect on serum PTH was also seen at 224pg/ml (baseline after wash-out, 316pg/dl, p<0.0001). Statistically significant reductions were seen with both total cholesterol and LDL cholesterol while HDL cholesterol and triglycerides were unchanged.

A study by Goldberg et al. looked at the effect of sevelamer HCL on serum phosphorus, calcium and PTH for patients with end-stage renal disease.[20] A 2 week washout, pre and post treatment with sevelamer HCL, was initiated with patients to determine the effect on the specified end-points. Patients were dose-titrated to achieve desired serum phosphorus control. The mean reduction in serum phosphorus was -1.4mg/dL, p=0.0001 with the majority of patients requiring 2-4 capsules three times daily. No statistically significant change in serum calcium level was seen. PTH levels after washout (395pg/ml) dropped to 283pg/ml after sevelamer HCL treatment.

Lanthanum:

Sprague and colleagues published the results of a randomized, double-blind, placebo-controlled trial with a focus on safety and efficacy of lanthanum in CKD stage 3 and 4 patients.[21] Patients with a baseline serum phosphorus level of >4.6mg/dL were randomized to receive lanthanum or placebo. There was a trend towards improvement in the lanthanum versus placebo with respect to serum phosphorus levels $\leq$4.6mg/dL (44.6% vs. 26.5%, p=0.12). Serum PTH decreased from baseline with the lanthanum group (23.8 $\pm$ 8.6pg/ml) and increased in the placebo group (8.8 $\pm$ 11.0 pg/ml; p=0.02). A small increase in serum calcium was seen in the lanthanum group with a small decrease with placebo (p=0.02). A statistically significant reduction in urinary phosphorus excretion was seen in the lanthanum group versus placebo (p=0.04). The safety and tolerability of lanthanum in this population was similar to that of placebo.

An article published by Wilson et al. compared lanthanum to “standard therapy” with the primary endpoint of survival.[22] This was an open-label, parallel-group, active comparator-controlled study of adult patients on hemodialysis. Patients were randomized to receive lanthanum or resume their previous phosphate binder regimen if serum phosphorus was >5.9mg/dL. Doses for each group were titrated to maintain serum phosphorus level $\leq$ 5.9 mg/dL and patients were followed for 2 years. The results yielded similar survival rates (19.9% patients died on lanthanum; 23.3% patients on standard therapy died; p=0.18). A sub-group of patients >65 on lanthanum had a greater benefit in survival as compared to placebo (27% vs. 39.3%; p=0.04), but this study was not designed to detect this outcome.

Hutchison and colleagues published the results of a long-term (up to 6 years) safety and efficacy study with lanthanum carbonate.[23] Ninety-three hemodialysis patients from 4 previous studies enrolled in this study. “Two-thirds of all patients received (lanthanum) doses of 2250 or 3000 mg/day.” Serum phosphate and calcium x phosphate product reductions were maintained up to 6 years. Therapy was also well tolerated without new or unexpected adverse effects.

The Fosrenol Overview Research Evaluation Study for Early Experience (FORESEE) study group published the results of its study that assessed the efficacy of higher dosed lanthanum (reformulated 250mg, 500mg, 750mg and 1000mg tablets).[24] Patients who did not achieve serum phosphorus control at 4 weeks were randomized to receive lanthanum 3000mg, 3750mg or 4500mg/day (cohort B) and were followed out to 4 months. Fifty-four percent of patients were included in cohort A (target achieved ≤ 3000mg/day). Cohort B yielded "control rates of 23, 38, and 32% for patients who were randomly assigned to 3000, 3750, or 4500mg/day." No statistically significant difference was seen with titrating to higher doses, but a trend was noted by the authors. The most commonly encountered adverse effects were GI and no increase in adverse effects was noted with higher doses of lanthanum.

A placebo-controlled, randomized, double-blind, parallel study of dialysis patients was published by Shigematsu and colleagues.[25] The primary endpoint was change in serum phosphate from baseline. Secondary endpoints were achievement of target serum phosphorus (≥ 3.5mg/dL and ≤5.5 mg/dL), time to achieve target, corrected serum calcium, calcium x phosphate product and serum PTH. Patients were randomized into 1 of 5 groups, lanthanum 750mg, 1500mg, 2250mg and 3000mg or placebo and followed for 6 weeks. The lanthanum group had significantly greater reductions in serum phosphorus versus placebo. Greater reductions were seen at higher doses, but the effect reached a plateau at 2250mg (82% reached target). Serum calcium levels decreased during the washout period (patients previously on calcium-based phosphate binders) and remained unchanged. There was a dose-dependent effect with adverse effects with GI related effects being most common.

Hutchison et al. published the results of the 3 year results for the tolerability and safety of lanthanum.[26] Patients who had completed a 6 month study (lanthanum versus calcium carbonate) were eligible to enter a 24 week, open-label extension. An additional group had the option to enter a 2-year extension. Serum phosphorus, calcium, PTH, vitamin D and calcium x phosphate product were assessed. Adverse effects were also followed. Serum phosphate control was maintained throughout the trial (63.3 % after 6 months, 54.4% at 2 years). Calcium x phosphate values over the 2 year extension "did not exceed the value recommended by the 2003 K/DOQI guidelines." Hypercalcemia was seen in 2.7% of cases compared to 20.2% during the double-blind phase. Gastrointestinal side effects were the most frequently encountered.

Results from Finn and colleagues describing the safety and efficacy of lanthanum on serum phosphorus for patients on dialysis.[27] This study had a single-blind, placebo run-in followed by a double-blind, placebo controlled phase in which patients would receive placebo or lanthanum in doses of 225, 675, 1350 or 2250 mg daily for 6 weeks. The primary endpoint for this study was serum phosphorus after 6 weeks of therapy. Secondary endpoints were: determination of effective lanthanum dose, timing of phosphorus reduction, safety and tolerability and serum calcium and PTH effects. This study found significant phosphorus reductions at doses of 675, 1350 and 2250mg/day with greatest benefit from the 1350 and 2250mg doses. The 1350mg/day dosing led to significant reductions at 2 weeks while benefits were seen with the 2250mg dosing at 1 week. Gastrointestinal disturbance was most frequently described, but was overall well tolerated.

Joy and colleagues published the results of their phase III study.[28] This was a randomized, double-blind, placebo-controlled, dose titration, 16 week study of dialysis patients and assessed the effect (efficacy and tolerability) of lanthanum on serum phosphorus, calcium, calcium x phosphorus and PTH. After washout, patients received lanthanum for 6 weeks with doses titrated to achieve serum phosphorus levels ≤5.9mg/dL. Over 70% of patients in this study received either 2250 or 3000mg to achieve target serum phosphorus levels. Patients were then randomized to placebo or lanthanum for a 4 week maintenance phase. Lanthanum showed statistically significant improvements in serum phosphorus, calcium x phosphorus and PTH levels ($p < 0.0001$, < 0.0001, < 0.01). Additionally, adverse event rates were similar between groups.

Head-to-Head:
While several trials focused on head-to-head treatment of either sevelamer or lanthanum with a calcium salt comparator, few trials are available comparing the two non-calcium containing phosphate binders.

A 2009 article by Sprague and colleagues compared the effect of sevelamer versus lanthanum on serum phosphorus levels in hemodialysis patients.[29] After a 2-3 week washout, patients with elevated serum phosphorus levels (≥6 mg/dL) and calcium (≥ 8.4mg/dL) underwent randomization. Patients received lanthanum carbonate 2250 to 3000mg/day or sevelamer HCL 4800 to 6400mg/day for 4 weeks, then had a second washout before switching to the other phosphate binder for 4 weeks. Serum phosphorus was reduced in both groups (intent-to-treat; lanthanum 1.7 ± 0.1mg/dL, sevelamer 1.4 ± 0.1mg/dL; p=0.113). A secondary per-protocol analysis revealed a statistically significant reduction in favor of lanthanum (-0.5mg/dL; p=0.007). Of note, this was a secondary analysis and should be viewed as such.

ADVERSE EVENTS:[7-10]

Calcium acetate:

-Mild hypercalcemia (serum calcium: >10.5mg/dL to ≤12 mg/dL)-may be asymptomatic or manifest as constipation, anorexia, nausea and vomiting
-Severe hypercalcemia (serum calcium: >12mg/dL)-confusion, delirium, stupor and coma
-Pruritis

Sevelamer (carbonate/hydrochloride):

-Dermotologic: pruritus
-Gastrointestinal: Vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence and constipation
-Neuromuscular: limb pain, arthalgia
-Respiratory: nasopharyngitis, bronchitis
-Note: Postmarketing surveillance revealed rare instances of fecal impaction, ileus, intestinal obstruction, intestinal perforation and rash.

Lanthanum carbonate:

-Gastrointestinal: Nausea, vomiting, abdominal pain
-Miscellaneous: Dialysis graft occlusion

-Long-term studies also revealed diarrhea, constipation, headache and hypercalcemia

PRECAUTIONS/CONTRAINDICATIONS: [7-10]

Calcium acetate:

-Contraindicated in patient with hypercalcemia or renal calculi
-Gastrointestinal effects (constipation, bloating and gas)
-Digitalis; potential risk for cardiac arrhythmia with hypercalcemia

Sevelamer (carbonate/hydrochloride):

-Contraindicated in patients with bowel obstruction
-Caution in patients with GI disorders
-Monitor serum chemistries
-Monitor for reduced vitamins D, E, K and folic acid (preclinical studies in animals with 6-10 time the human dose.)

Lanthanum carbonate:

-Caution in patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction
-Caution with abdominal x-rays as lanthanum may give a radio-opaque appearance.

LOOK-ALIKE/SOUND-ALIKE ERROR RISK POTENTIAL: [30-31]

PhosLo® can be confused with Phos-Flur®, ProSom
Renagel® may be confused with Reglan®, Regonol®, Renal Caps, Renvela ®
Renvela® may be confused with Reglan®, Regonol®, Renal Caps, Renagel®
Sevelamer may be confused with Savella®
Lanthanum may be confused with lithium

DRUG INTERACTIONS: [7-10, 30]

Calcium acetate:

Tetracyclines: may decrease bioavailability with tetracyclines
Bisphosphonates: calcium salts may decrease the absorption of the bisphosphonate
Calcium Channel Blockers (CCB's): calcium salts may diminish the therapeutic effect of CCB's
Quinolone antibiotics: calcium salts may decrease the absorption of quinolone antibiotics with the expection of moxifloxicin
Eltrombopag: calcium salts may decrease the serum concentration of eltrombopag
Thiazide diuretics: calcium salts may decrease the excretion of calcium salts.
Thyroid products: calcium salts may diminish the therapeutic effect of thyroid products.
Trietine: calcium salts may decrease serum trietine levels and trietine may decrease serum concentration of calcium salts

Sevelamer (carbonate/hydrochloride):

Ciprofloxacin: decrease in ciprofloxacin bioavailability (~50%)
Levothyroxine: may decrease the serum concentration of levothyroxine
Mycophenolate: may decrease the serum concentration of mycophenolate

Lanthanum carbonate:

No significant drug interactions noted
Recommended to take medications subject to reduced absorption with when co-administered with antacids should not be taken within 2 hours of dosing with lanthanum (i.e.antibiotics, thyroid hormones, ACE-inhibitors, statins, and anti-malarials

CONCLUSIONS:

1. How do the calcium and non-calcium containing phosphate binders compare in effectiveness clinically in the treatment of CKD related hyperphosphatemia?

The current body of literature appears to show the both the calcium and non-calcium containing phosphate binders would be considered comparable for its benefit in improving serum phosphorus levels. Each binder type shows benefit to calcium x phosphate product. No single product appears to be clinically or statistically superior.

2. How do the calcium and non-calcium containing phosphate binders compare in terms of safety/tolerability in patients with hyperphosphatemia?

It appears that each of the products are relatively well-tolerated based upon placebo based trials as well as the trials comparing calcium salts to the non-calcium containing phosphate binders. Gastrointestinal disturbance remains the most frequently encountered adverse effect of each of the products available from both classes. No product appears to be superior in terms of safety/tolerability.

3. How should the calcium and non-calcium containing phosphate binders be best utilized in the treatment of hyperphosphatemia?

As the data has failed to show that non-calcium containing phosphate binders are superior in efficacy or safety, it seems that calcium salts should be considered the workhorse phosphate binder for patients in which serum calcium is within normal limits. Those patients who have hyperphosphatemia and hypercalcemia and are on dialysis should have a non-calcium containing phosphate binder available.

RECOMMENDATIONS:

Based upon the data available, it seems reasonable to have calcium-based phosphate binders as the regimen of choice for patients without elevations in serum calcium. Since the available data has not shown a clearly superior non-calcium containing phosphate binder, it seems reasonable to consider adding the class to the NCF and potentially consider the addition of a named product based upon the available pharmacoeconomic and IHS use data.

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