CONTACT HOUR: 2.0 HRS

‘Phos’ing over phosphorus: A primer on updates in phosphate binders

By Franky Liu and Maeghan Pemas

ABSTRACT

Addressing serum phosphorous in patients with ESRD remains a challenging balancing act of appropriate pharmacological treatment. Multiple agents are available for binding dietary phosphates in attempts to maintain a harmony of serum phosphorous and other important factors in CKD-MBD, such as calcium and parathyroid hormone. In this brief primer, we aim to compare, discuss, and share clinical experience of different phosphate binders, old and new, and to discuss what research has yet to address in current clinical practice. Guidelines and best practices in CKD-MBD are also briefly reviewed. This primer concludes with reviewing a novel iron-based phosphate binder, succroferic oxyhydroxide (SO), and its perceived current place in therapy.

“Serum phosphorus” or “serum phosphate”—regardless of which clinical synonym one uses, practitioners arguably spend countless hours educating patients on the clinical significance and management of chronic kidney disease-associated mineral and bone disorders (CKD-MBD). Perhaps this is rightfully so – renal osteodystrophy is associated with increased bone fracture rates, with hip fractures in particular leading to significant morbidity and mortality (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group (2017). In fact, one study suggests that every 0.33 mmol/L increase in serum phosphorus is correlated with an 18% increase in mortality (Palmer et al., 2011). Experts have also suggested correlations with cardiovascular disease, possibly due to increased vascular and valvular calcification, although evidence of these associations is still uncertain (Adeney et al., 2009).

AUTHOR NOTE

Franky Liu, BScPhm, MSc, RPh, Clinical Pharmacist – Nephrology, Halton Healthcare Services, Oakville, ON; Maeghan Pemas, BScPhm, RPh, Clinical Pharmacist – Nephrology, Halton Healthcare Services, Oakville, ON

Correspondence concerning this article should be forwarded to: Franky Liu, Halton Healthcare Services, 3001 Hospital Gate, Oakville, ON L6M 0L8.
Tel: (905) 845-2571 ext 6521. Fax: (905) 338-4498.
*Email: **fliu@haltonhealthcare.com***

At its core, osteocytes undergo a homeostatic cycle of bone resorption and ossification, collectively referred to as bone turnover. Disharmony of this cycle occurs with elevated serum phosphorous, which causes nodular hyperplasia secondarily from cacophonic phosphorus stimulation of the parathyroid. This results in increased serum PTH, which cascades to abnormal bone formation, and ultimately to osteoporosis or osteopenia (Hruska et al., 2008).

The management of CKD-MBD, while at times laborious, is a crucial puzzle piece in the comprehensive care of patients with end-stage renal disease (ESRD). Its complexities usually call for “all hands on deck”, often requiring the patient and their care team to make complex and drastic lifestyle changes, along with meticulous handling of dialysate bath concentrations.

WHAT ARE OUR NEPHROLOGY COLLEAGUES DOING NOW?

Nephrology health workers may look to the Kidney Disease Improving Global Outcomes (KDIGO) organization to guide treatment and management of the complexities that come with ESRD. In their 2017 update, KDIGO had recommended steering treatment based on serial assessments of phosphorus, calcium and PTH in concert, specifically lowering high serum phosphorous while maintaining calcium levels with an age-appropriate normal range (KDIGO Working Group, 2017). In particular, a retrospective observational study found an increased mortality risk with either hypocalcemia (less than 2.10 mmol/L) or hypercalcemia (greater than 2.75 mmol/L) over time. Contrarily, although there is an increased time-dependent mortality risk with low phosphorus (less than 1.13 mmol/L), mortality risk with high phosphorus (greater than 1.78 mmol/L) remains unclear (Floege et al., 2011).

Diligent case management therefore necessitates a multidisciplinary, multifactorial approach. Congruent with the KDIGO guidelines, dietary modifications, with particular consideration of dietary source of phosphates, act as one facet of care (Liu et al., 2013). That is, since not all phosphate sources are equal (i.e., inorganic phosphate sources from animal products and additives are generally more

bioavailable than vegetable sources), careful dietary assessments could supplant many hyperphosphatemia woes (Hruska et al., 2008). Current evidence on its efficacy is still uncertain, and it is believed that, over time, dietary modifications will unlikely serve as the sole treatment regimen for hyperphosphatemia. Pharmacotherapy is often required.

Calcium-Salt Phosphate Binders

Patients are often started on calcium-salt binders, such as calcium carbonate in flavoured chewable (such as Tums™) or regular tablets, as an inexpensive and readily accessible choice of therapy. These binders are activated by gastric acid, which then precipitates dietary phosphate into the gastrointestinal tract. Although ubiquitous and generally safe at low doses, calcium-based binder tablets are usually numerous and/or bulky, often perceived as "difficult pills to swallow" both literally and figuratively. Furthermore, these binders are not ideal in patients at risk of hypercalcemia; in fact, doses surpassing 2 g in a day have been associated with vascular calcification (Hutchison, 2009; KDIGO Working Group, 2017). Alternative non-calcium-based binders may be preferred in patients with high-normal to high serum calcium levels.

Polymeric Non-Calcium Phosphate Binders

Binders such as sevelamer hydrochloride (Renagel™) or sevelamer carbonate (Renvela™) tablets/lightly citrus-flavoured powders for oral suspension are calcium-free, evading hypercalcemia while offering a means of reducing dietary phosphate absorption. Sevelamer is a non-absorbable and fat-soluble synthetic polymer that, when activated by gastric acid, weakly complexes with dietary phosphate (Hutchison, 2009). This weaker interaction makes sevelamer less potent than calcium-salt binders, translating to a higher pill or liquid volume burden (Daugirdas et al., 2011); this, combined with its exorbitant cost, may be less accessible to patients without full drug insurance coverage. Other considerations include binding of fat-soluble vitamins when taken together, and risk of metabolic acidosis. Interestingly, because of its fat solubility, some studies have suggested that sevelamer may decrease LDL-C and total cholesterol, with some studies reporting up to 36% reduction; this may be congruent with associations with decreased risk of coronary and aortic calcification (Nikolov et al., 2006). Given the potential complexities in drug administration and potential high pill/volume burden, other solutions may be available to overcome these hurdles.

Other Metallic-Salt Phosphate Binders

Historically and perhaps more acutely, practitioners have used aluminum hydroxide as a phosphate binder. With approximately double the potency of calcium salts and non-reliance on gastric acidity, these could be effective in very short-term therapy in patients also with hypercalcemia (Daugirdas et al., 2011; Hutchison, 2009). However, there is no official safe dose or level of aluminum, with potential risk of fecal impaction and encephalopathy (KDIGO Working Group, 2017).

In contrast, lanthanum, which is similarly trivalent cationic as aluminum, seems to have an acceptable safety profile while binding dietary phosphate at the same potency. Because of this, patients usually require fewer tablets for a greater decrease in serum phosphorus than calcium-salt or polymeric binders (Daugirdas et al., 2011). Formulated as a carbonate in a tasteless chewable tablet (Fosrenol™), lanthanum readily forms insoluble salts with phosphate without acid, leading to less variability caused by gastric acidity. A near-infinitesimal amount does get absorbed, which seems to bind plasma proteins and eventually get excreted through bile; some long-term studies have suggested low levels associated with treatment in ESRD are not associated with any long-term toxicity (Hutchison, 2009). However, because it forms very insoluble salts when bound to phosphate, patients may experience constipation. This may rarely lead to bowel obstruction and colonic perforation, reinforcing its relative contraindication in history of bowel obstruction and decreased bowel peristalsis (Hutchison, 2009). Moreover, lanthanum, being a rare earth metal, is generally expensive, which may be inaccessible to patients not covered by an insurance plan, ineligible for product coverage, or both.

WHAT WERE THE GAPS IN RESEARCH AND THERAPY?

So far, research has suggested that there is some decrease in mortality with use of any phosphate binder, although at the time of this primer, no binder has demonstrated superiority over others. There is also clinical uncertainty if there is any benefit to combining non-calcium binders. One study suggests that combining lanthanum and sevelamer leads to serum phosphorus reductions similar to monotherapy with either agent. These findings raise questions about possible antagonistic pharmacodynamic interactions between binders (Senatore et al., 2011).

In clinical treatment, each therapy mentioned so far appears to have their own mix of pros and cons; practitioners may encounter patients with specific combinations of contraindications with compromises that become difficult to balance. To illustrate, a patient with diverticular disease and gastroparesis, simultaneously with swallowing issues (for which high pill burden or large liquid volumes are intolerable), hypercalcemia, and hyperphosphatemia absent of other confounders may be left without any good option. One would need to consider the risk of obstruction if deciding on lanthanum; risk of non-adherence or choking on sevelamer; risk of aluminum toxicity with aluminum hydroxide; or risk of fatal hypercalcemia with calcium carbonate. Therapies with a different mix of efficacy and safety considerations are needed to relieve this therapeutic "deadlock".

WHAT ABOUT IRON-BASED PHOSPHATE BINDERS?

As of recent, sucroferric oxyhydroxide (SO, Velphoro™) was the first iron-based phosphate binder officially approved for hyperphosphatemia in Canada. Supplied as flavoured chewable tablets containing 500 mg of elemental iron equivalent (or 2,500 mg of drug; dosages are usually expressed based on equivalent iron content), SO is an insoluble complex of sucrose and iron stabilized with starch that strongly binds with dietary phosphate (Vifor Fresenius Medical Care Renal, 2019).

Because this entire chemical complex is virtually insoluble in water, very little of its constituents (particularly iron) get absorbed. More specifically, pharmacokinetic studies

found only a median of 0.04% w/w of iron was actually absorbed after chronic dosing after 21 days; interestingly, however, healthy volunteers did absorb approximately 10 times more iron than the CKD group, possibly owing to the lower serum ferritin and/or compensatory hepcidin release that would otherwise impair oral iron absorption in patients with ESRD (Canadian Agency for Drugs and Technologies in Health [CADTH], 2019).

HOW DOES SUCROFERRIC OXYHYDROXIDE (SO) COMPARE TO OTHER BINDERS?

One extension of an open-label, multi-centred, active-controlled study showed non-inferiority to sevelamer at all points of its study for patients on hemodialysis(treatment difference in change from baseline phosphorus –0.04 [-0.12, 0.04], p = .293) (Floege et al., 2015; Vifor Fresenius Medical Care Renal, 2013). Patients were titrated from a similar baseline hyperphosphatemia over eight weeks, with either SO 1,000-3,000mg (two to six tablets daily) or sevelamer 2,400-14,400mg (three to 18 tablets daily). Participants were then monitored, with minor adjustments in dose based on tolerability over four weeks. The study was extended for 12 additional weeks with dose fine-tuning (CADTH, 2019; Vifor Fresenius Medical Care Renal, 2013, 2019). Another one-year open-label study showed similar results in patients on peritoneal dialysis (-0.6 mmol/L change from baseline phosphorous for both groups, p = .53) (Floege et al., 2017).

At a glance, it might appear that SO may require fewer tablets than sevelamer to elicit a similar response, although the translatable difference in average and median number of tablets from either group is unclear. Furthermore, formal quantitative dose conversions between SO and other binders has not yet been studied. Patients with disorders that affect gastric acid may respond differently by the binder chosen. SO and lanthanum, for instance, are unaffected by gastric acidity. However, patients with hypochlorhydria may respond inadequately to sevelamer or calcium-based binders (CADTH, 2019). Importantly, patient preference in therapy may also be a matter of taste. SO is strongly woodberry-flavoured and sweetened with neohesperidin to mask its metallic taste; despite this, some patients may still notice an unpleasant aftertaste (Vifor Fresenius Medical Care Renal, 2019). This contrasts to lanthanum carbonate and film-coated sevelamer tablets, both of which are virtually flavourless.

WHEN MIGHT SO BE AN ALTERNATIVE FOR PATIENTS?

SO is officially indicated for treating hyperphosphatemia in patients 18 years or older with ESRD on either peritoneal dialysis or hemodialysis. This iron-based binder might serve as an alternative when other binders are inadequate or intolerable, or when a patient also has hypercalcemia. Patients with hypochlorhydria that are refractory to other binders may respond better to SO (Vifor Fresenius Medical Care Renal, 2019); causes of hypochlorhydria could include specific pathologies, or concomitant therapy with high-dose proton-pump inhibitors or other acid reducers. In addition, SO may be preferred over lanthanum in patients with other gastrointestinal issues, such as history of bowel obstruction or chronic constipation (Hutchison, 2009).

WHEN SHOULD I *NOT* CONSIDER SO?

Although studies suggest that absorption is insignificant, monographs still list haemochromatosis or other iron accumulation disorders as contraindications. Patients with evidence of iron overload (e.g., excessively elevated serum ferritin or a transferrin saturation greater than 50%) should not be started on SO, and caution should be exercised if deciding to continue pre-existing therapy. Also, though no allergic reactions have yet been reported, patients allergic to any component of its formulation, such as maize or potato starch, or the drug itself should not take SO (Vifor Fresenius Medical Care Renal, 2019).

Practitioners should note that SO has not yet been studied in hepatic disease or patients with peritonitis (for which any iron treatment should be avoided). Clinical decisions to continue therapy require careful balance of risk and benefit (Vifor Fresenius Medical Care Renal, 2019).

Practitioners should also note that, particularly for patients who recover from dialysis or receive a transplant, SO has not been studied in CKD patients not on dialysis; continuing therapy would therefore be off-label.

WHAT SHOULD I MONITOR IF SO THERAPY IS INITIATED?

Similar to the usual management of CKD-MBD, serum calcium, phosphorous, and PTH should be monitored at least every one to three months, or more frequently if deemed necessary. Iron studies, ferritin, and transferrin saturation could be added if a patient has been historically responsive to oral iron therapy and/or is at imminent risk of iron overload (KDIGO Working Group, 2017). Of interesting note, although increased serum calcium from treatment seems unlikely, patients with hyper- or hypocalcemia were excluded from major studies with SO; response from these patients is uncertain at this time.

Patients will sometimes experience side effects upon starting, most of which are GI-related like diarrhea. These are usually self-limiting, and will resolve with time, and are minimal if SO is titrated weekly in 500 mg increments. Doses generally start at 500 mg three times daily with meals for most patients. Dark stools are also common since SO is not absorbed, although this will not interfere with fecal occult blood testing (FOBT) if a patient is due to repeat a test while on therapy (Vifor Fresenius Medical Care Renal, 2019).

In addition to its metallic aftertaste as mentioned, SO may also discolour teeth and mucous membranes to an orange-brown colour: this should be rinseable with water. Patients may hold the medication if the colour remains despite rinsing. So far it is uncertain if progressive use leads to irreversible staining, although literature from the manufacturer suggests this is likely benign (Vifor Fresenius Medical Care Renal, 2019).

Patients concomitantly on oral bisphosphonates, tetracyclines (including doxycycline), and levothyroxine/thyroid hormones, whether pre-existing or added in the future, should space administration away by at least one hour. These drug classes are potentially inactivated in the presence of divalent cations such as iron. However, these

interactions have not yet been proven outside of in vitro testing. Interestingly, however, in vitro testing showed no interaction with ciprofloxacin, although other fluroquinolones were not tested (Vifor Fresenius Medical Care Renal, 2019).

WHAT SHOULD WE KNOW ABOUT ACCESSIBILITY AND COVERAGE?

Based on recommendations by CADTH (2019), SO appears on provincial formularies as an exceptional access benefit. Clinical criteria indicated for coverage are similar to sevelamer and lanthanum, and will require case-by-case approval through specific provincial health ministries. Patients with private insurances should also have coverage for SO, but some may require prior authorization paperwork before reimbursement; pharmacists and social workers can facilitate arranging additional paperwork if required.

In the event that patients must pay out-of-pocket, SO averages approximately $416 monthly. This contrasts to sevelamer hydrochloride ($450), sevelamer carbonate ($286), lanthanum carbonate ($214), or calcium carbonate ($54) (CADTH, 2019). Practitioners should also be aware that sevelamer carbonate powder for oral suspension formulations may not be listed in some provincial exceptional access benefits.

WHAT ARE SOME QUESTIONS STILL LEFT UNANSWERED?

Although SO adds yet another tool to our arsenal for treating hyperphosphatemia, the relative potency of SO from other binders is not yet clear. Literature seems to suggest that SO has at least equal or less pill burden compared to sevelamer. Also unclear is the effect of SO and other non-calcium-based binders on all-cause mortality, and/or risk of vascular calcification. Some small-scale studies suggest that sevelamer exacerbates aortic calcification less frequently than calcium-based binders; further larger-scaled studies are needed (Block et al., 2005).

As we obtain more experience with the use of these various phosphate binders with time, we may learn more about post-marketing effects of SO, in addition to any ancillary benefits or risks not yet studied prior to approval. Nonetheless, SO may find further niche uses as we share more clinical experiences within our network of nephrology professionals. After all, we all collectively have a "bone to pick" with persistently elevated serum phosphorous levels; new and developing solutions will hopefully ease some common discussion points in patient care and bloodwork rounds.

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CONTINUING EDUCATION STUDY QUESTIONS **CONTACT HOUR: 2.0 HRS**

‘Phos’ing over phosphorus: A primer on updates in phosphate binders

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1. Patients should have phosphorous targeted to appropriate levels based on degree of renal impairment for the following reasons:
   a) Increased mortality risk with hypophosphatemia
   b) Decrease bone fracture rate by avoiding hyperphosphatemia
   c) Increased mortality risk with hyperphosphatemia
   d) A and B
   e) All of above

2. 63-year-old female (dialysis vintage 3 years) with normocalcemia; hyperphosphatemia. Renal dietitian has assessed and would prefer not to restrict diet d/t limited intake. Currently on lanthanum 500 mg tid. Patient unable to increase d/t constipation at higher doses. PMHx does not reveal any significant GI disorders. Patient pays for meds out-of-pocket. Most appropriate course of action for treating CKD-MBD includes:
   a) Titrate lanthanum (Fosrenol™) to higher dose with scheduled Senokot 17.2 mg qhs
   b) Switch to sucroferric oxyhydroxide (Velphoro™)
   c) Switch to CaCarb 500 mg tid cc (or Tums™ product if patient prefers chewable)
   d) Switch to aluminum hydroxide
   e) Switch to sevelamer hydrochloride (Renagel™)

3. 55-year-old male (dialysis vintage 1 year) with Hx failed renal transplant 10 years ago on mycophenolate mofetil 500 mg bid. Mildly low calcium; hyperphosphatemia. Other blood work of note includes Hgb 94. TSAT 15%. Ferritin 250. Patient has private drug coverage. BEST option for treatment:
   a) Lanthanum (Fosrenol™)
   b) Sevelamer hydrochloride (Renagel™) (with separation from Cellcept™ doses by 2 hours)
   c) Calcium (with separation from Cellcept™ doses by 2 hours)
   d) Succoferric oxyhydroxide (Velphoro™) (help with iron levels as well) with separation from Cellcept™ doses by 2 hours
   e) Switch to aluminum hydroxide

4. 70-year-old female (dialysis vintage 3 years) on pantoprazole 40 mg bid (Zollinger-Ellison syndrome) with hypercalcemia; hyperphosphatemia. Also has PMHx bowel perforation. BEST option for treatment:
   a) Calcium
   b) Sucroferric oxyhydroxide (Velphoro™)
   c) Lanthanum (Fosrenol™)
   d) Sevelamer hydrochloride (Renagel™)
   e) Sevelamer carbonate (Renvela™)

5. 85-year-old male (dialysis vintage 10 years) with hyperphosphatemia; normocalcemia. Patient is unable to swallow tablets whole. Relevant PMHx includes calciphylaxis (approx. 14 mos ago; now in remission) and chronic constipation.
   a) Calcium
   b) Sucroferric oxyhydroxide (Velphoro™)
   c) Lanthanum (Fosrenol™)
   d) Sevelamer carbonate (Renvela™) (as powder for suspension)
   e) B or C

6. In comparing sucroferric oxyhydroxide to sevelamer hydrochloride (Renagel™) in clinical trials, Velphoro™:
   a) Showed superior phosphate control
   b) Had more favorable side effect profile
   c) Shown to be non-inferior to sevelamer hydrochloride (Renagel™)
   d) Showed inferior phosphate control with increased side effects
   e) Showed inferior phosphate control with improved side effect profile

7. Which phosphate binder(s) are indicated in treatment of hyperphosphatemia in pre-dialysis patients?
   a) Calcium
   b) Sevelamer (Renvela™ and Renagel™)
   c) Lanthanum (Fosrenol™)
   d) Sucroferric oxyhydroxide (Velphoro™)
   e) A, B and C

8. Appropriate counselling point(s) for Velphoro™ include:
   a) GI side effects (diarrhea)
   b) Black stool
   c) Can discolour teeth – rinse with water
   d) Metallic aftertaste
   e) All of the above

9. Which of the following statements is TRUE:
   a) Calcium and lanthanum should not be used first-line in patients with acid hypersecretory disorders
   b) Calcium and sucroferric oxyhydroxide administration should be separated from levothyroxine
   c) Aluminum hydroxide fell out of common usage d/t decreased effectiveness in comparison with calcium
   d) Elemental calcium in doses greater than 3 g / day have been associated with vascular calcification
   e) Combining sevelamer hydrochloride (Renagel™) and lanthanum (Fosrenol™) has shown superior efficacy compared with combining sevelamer hydrochloride (Renagel™) and calcium

10. 49-year-old male (dialysis vintage 8 years) with hyperphosphatemia requiring treatment. Patient also has GI disease, metabolic acidosis, and hypercalcemia. Most appropriate treatment option:
    a) Calcium tid cc (less absorption with meals)
    b) Lanthanum (Fosrenol™)
    c) Sucroferric oxyhydroxide (Velphoro™)
    d) Sevelamer hydrochloride (Renagel™)
    e) Diet restrictions only

CONTINUING EDUCATION STUDY ANSWER FORM

CE: 2.0 HRS CONTINUING EDUCATION

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6.	a	b	c	d	e
7.	a	b	c	d	e
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9.	a	b	c	d	e
10.	a	b	c	d	e

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