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clinicalnotes™

Optimizing Phosphorus Control in Chronic Kidney Disease

Chronic kidney disease (CKD) is the most frequent cause of hyperphosphatemia in adult dogs and cats, as phosphorus retention occurs due to impaired renal phosphate excretion.[1] Hyperphosphatemia is associated with CKD progression and decreased survival.[2]

KEY POINTS

- Progression of renal disease and decreased survival times are associated with hyperphosphatemia.
- Renal diets are often recommended at the onset of kidney disease, but the addition of phosphate binder supplements can potentially minimize disease progression.
- Intestinal phosphate binders for dogs and cats are frequently underutilized.
- Naraquin™ is formulated to provide a balanced approach to phosphorus binding, with a proprietary blend of 3 phosphate binders: ferric citrate, calcium acetate, and chitosan.
- The omega-3 fatty acids and β-glucans found within Naraquin™ are designed to support renal health.
- Evaluated in healthy cats on a maintenance diet, Naraquin™ has demonstrated the ability to reduce urine phosphorus levels.

In early stages of CKD (IRIS stage 1),[3] serum phosphorus remains within the reference range due to compensatory increases in the secretion of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23). In advanced stages of CKD, serum phosphorus can increase above the reference range as compensatory changes are overwhelmed.

Circulating phosphorus concentrations depend on dietary phosphorus intake, GI absorption, translocation into intracellular sites, skeletal resorption, and urinary phosphorus excretion.[1] The kidneys are crucial in regulating circulating phosphorus concentrations within a narrow range.[4] The typical reference range for phosphorus is 2.5-5.5 mg/dL (0.8-1.8 mmol/L) for mature dogs and 2.5-6 mg/dL (0.8-1.9 mmol/L) for cats.[5]

Methods for Reducing Total Body Phosphate Burden

Decreasing GI absorption of dietary phosphorus decreases total body phosphate burden. Diets with lower phosphorus content (mg/100 kcal), diets with decreased phosphate bioavailability, and the addition of intestinal phosphate binders can help decrease phosphate.[6,7] Although dietary phosphorus restrictions can be effective initially, phosphate binder supplements can be a critical addition or replacement for renal diets.[8,9]

Intestinal Phosphate-Binding Agents

Phosphate-binding agents trap phosphorus in the gut and increase insoluble phosphate salt excretion through the feces.[8] Intestinal phosphate binders work best when given with food or within 2 hours of feeding.[10] Administration should be based on meal size (ie, phosphorus intake) and individual serum phosphorus levels and titrated to effect.[1,10] Achieving mid-reference range target phosphate concentrations can be challenging in those with higher levels of azotemia due to severe decreases in GFR and phosphorus retention.

Aluminum-Containing Binders

Aluminum salts are frequently used in phosphate binding. Citrate salts, however, enhance aluminum absorption and should be avoided.[11] Some dogs with azotemic CKD treated with aluminum salts have been shown to have mean circulating alumi-

num concentrations significantly higher than the reference range, with some dogs showing neuromuscular signs[2,12-14]; in these dogs, progressive decline in mean corpuscular volume and mean corpuscular hemoglobin was a sensitive and specific biomarker for aluminum accumulation.[14,15] Aluminum toxicity may be of more concern in cats due to their longer survival times, but this has yet to be reported. Constipation is a common adverse effect.

Iron-Containing Binders

Iron-based phosphate binders can potentially correct anemia and decrease circulating phosphorus.[16] Ferric citrate can be helpful in phosphate binding and correcting anemia in humans with CKD.[17-19] Although traditional oral iron preparations are associated with frequent adverse GI effects and poor intestinal absorption,[18] ferric citrate is well tolerated in humans with CKD, with significant intestinal absorption of iron.[16] Discolored stool and constipation are the most common adverse effects.[16,17]

Studies have shown that ferric citrate can help reduce hyperphosphatemia.[18] An iron oxide/hydroxide insoluble complex was developed for cats as an oral intestinal phosphate binder[20,21]; when added to maintenance food and fed to healthy cats in a study,[21] urine phosphate concentration was significantly decreased, increased urine phosphate excretion was apparent, and fractional excretion of phosphate into urine developed in a dose-dependent manner. In healthy cats, significant decreases in serum phosphate, urinary phosphate, and urinary fractional phosphate excretion were observed in those treated with a renal diet supplemented with iron oxide/hydroxide. This iron-supplemented diet also resulted in more significantly reduced serum and urine phosphate concentrations than did the lanthanum-supplemented control group.[21]

Calcium-Containing Binders

Although their binding capacity is lower than aluminum salts, calcium-based salts have been used to avoid aluminum exposure.[10] Calcium carbonate binds phosphorus best in an acidic environment (pH, ≈5), with binding capacity reduced in the neutral pH range.[22] Calcium acetate, however, can bind phosphate over a wide range of pH levels and has greater phosphate binding capacity than calcium carbonate, reducing administration and the potential for hypercalcemia. Advantages of calcium salts include low costs and mitigation of hypocalcemia.[23] GI upset and constipation are common adverse effects.[11] When calcium-containing binders are used, ionized calcium concentration should be monitored, and use with calcitriol may be restricted.

Other Phosphate Binders

Chitosan, a nonabsorbable polysaccharide, can decrease oxidative stress, PTH, and phosphate serum markers in dialysis patients.[23] A combination of chitosan and 10% calcium carbonate has been shown to successfully decrease serum phosphorus in cats with early CKD.[24,25]

A multi-ingredient oral supplement designed to provide intestinal phosphate-binding from ferric citrate, calcium acetate, and chitosan currently marketed in the US for use in dogs and cats (Naraquin™) demonstrated positive results in a pilot study.[26] Omega-3 fatty acids and β-glucans are included for additional renal benefits. In this study, urinary phosphate concentration significantly declined at 1 and 4 weeks of administration in healthy cats.[26]

Sevelamer is a commonly used non-calcium–based phosphate binder but has a lower phosphate-binding capacity than other binders.[11] Effects of this binder in dogs and cats with CKD have not been reported. GI intolerance and high costs are some disadvantages.

Lanthanum carbonate is another non-aluminum and non-calcium intestinal phosphate binder.[10] Lanthanum's affinity for intestinal phosphate binding is similar to aluminum and about twice that of sevelamer or calcium-based binders.[27]

Toxicity studies in dogs have shown that lanthanum accumulates at low concentrations in many tissues (eg, GI, bone, liver) and has been studied extensively in normal and azotemic CKD cats. It is an excellent binder, with minimal to no recognized toxicity in cats[28-35]; however, expense can limit its use.

Conclusion

Dietary phosphate restriction is considered standard of care for dogs and cats with IRIS CKD stages 2 through 4. Serum phosphorus concentrations should be measured in CKD patients after 4 to 6 weeks of feeding a reduced phosphorus diet or starting a phosphate binder.

Some cats with CKD can develop total, ionized hypercalcemia during the long-term feeding of highly restricted phosphate renal diets. Thus, it is essential to measure ionized calcium when phosphorus is measured. If a patient is stable and the desired targeted circulating phosphorus levels have been reached, evaluating a renal panel that includes phosphorus and calcium is recommended every 3 to 4 months. Increased calcium trends can indicate too little phosphorus available in the gut lumen, favoring absorption of too much calcium into circulation, which is more likely to develop in cats with early-stage CKD.[36-40]

With many different phosphate binders available to choose from, it is important to have an understanding of the pros and cons of each option. Cost, adverse effects, and efficacy all play into the most appropriate choice for a patient. As new phosphate binders come to market, available options continue to expand, allowing for appropriately addressing and managing secondary issues in patients with CKD.

For references, please see **cliniciansbrief.com/article/clinical-notes-optimizing-phosphorus-control-chronic-kidney-disease**

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