

Medical Management of Hyperphosphatemia, Hypokalemia, and Acidosis in Chronic Kidney Disease

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Controlling metabolic derangements in patients with chronic kidney disease (CKD) such as hyperphosphatemia, hypokalemia, and metabolic acidosis are important to maintain a patient's quality of life for an extended period. Paramount to this therapeutic plan is feeding a diet designed specifically for patients with kidney disease. As the disease progresses through Stage II to Stage III and IV CKD often diet alone is insufficient to control these electrolyte disorders and additional therapeutic interventions are necessary. This lecture will focus on enteral therapies beyond diet that are beneficial in treating these metabolic abnormalities.

Hyperphosphatemia

Increased serum phosphate concentrations have been linked to higher mortality in dogs, cats, and people with chronic kidney disease. The observed hyperphosphatemia occurs secondary to an imbalance in gastrointestinal phosphate absorption, bone formation/resorption, and renal phosphate clearance. This imbalance occurs in early stages of CKD and if unaddressed can lead to renal secondary hyperparathyroidism. In patients with stage II, III, and IV CKD target serum phosphorus concentrations should be 3.5-4.5mg/dL, 3.5-5.0mg/dL, and 3.5-6.0mg/dL respectively. In veterinary patients, limiting serum phosphorus concentrations is primarily achieved by restricting the dietary consumption of phosphorus and the administration of oral phosphate binders. Phosphate binder dosing is usually performed to effect with second agents added as a patient nears a binder's maximal dose before toxicity is possible. Therapy is initiated at the lower end of each binder's dosing range and titrated upwards every 4-6 weeks until the serum phosphorus concentration is controlled. The efficacy of each binder at achieving this goal is variable and dependent on a number of characteristics unique to each binder.

Phosphate binders primarily exert their therapeutic effect by ionic binding or ion exchange. The former class of phosphate binders is primarily metal-based and contains two elements that disassociate within the gastrointestinal tract. One of the elements binds phosphate with high affinity to create an insoluble complex that is not absorbed by the body. The freed second element is then available to bind cations within the intestine such as hydrogen and frequently acts as an acid buffer thereby exerting a secondary effect of acidosis control. For most ionic binders a portion of disassociated elements fails to bind phosphorus and is systemically absorbed increasing the metal's accumulation within the body thereby eliciting toxic or occasionally beneficial effects depending on the binder used. Examples of ionic binding phosphate binders include aluminum hydroxide, calcium carbonate, calcium acetate, magnesium carbonate, lanthanum carbonate, ferric citrate, and sucroferric oxyhydroxide. Alternatively, ion exchange phosphate binders bind phosphate to a large cationic polymer by exchanging an ion such as chloride or bicarbonate for phosphorus. The insoluble polymer thus makes any bound phosphorus unavailable for absorption into circulation. Examples of ion exchange phosphate binders include sevelamer hydrochloride, sevelamer carbonate, and chitosan.

Aluminum hydroxide is one of the more common phosphate binders used in veterinary medicine since it binds phosphorus with a higher affinity than most other medications with the possible exception of lanthanum carbonate, is relatively inexpensive, and the toxic side effects preventing its use in human medicine are rare in dogs and cats at recommended dosages. Aluminum hydroxide is soluble at a wide range of pH allowing disassociation throughout greater lengths of the gastrointestinal tract compared with other drugs. The disassociation creates an aluminum ion capable of binding phosphorus as well as a hydroxide ion capable of reducing the body's acid load thereby allowing aluminum hydroxide to have a dual benefit in patients with CKD.

Calcium carbonate is another common phosphate binder given its low cost and dual effect of the carbonate acting as an acid buffer. One drawback to this binder is that it has reduced efficacy at a low pH however the calcium carbonate tablets dissolve best in an acidic pH resulting in greatest drug availability in an environment suboptimal to maximize phosphate binding. This

also means that patients on gastric acid suppressors may have reduced availability of calcium carbonate. Another obstacle to its use is the potential induction of hypercalcemia. This side effect is exacerbated by the co-administration of vitamin D analogues and hence calcium salts should not be administered to hypercalcemic patients or patients on calcitriol.

Lanthanum carbonate (Fosrenol) is a relatively new to veterinary medicine calcium-free phosphate binder. It has the advantage of binding phosphorus within a wide pH range and in animal studies lanthanum was comparable to aluminum salts in phosphate binding capacity. Largely insoluble, 93.4% of the drug is excreted in the feces of dogs after oral administration and hence side effects of lanthanum accumulation within the body are not currently reported in our patients. The greatest argument against the use of lanthanum carbonate is its high cost with limited proven survival benefit over less expensive alternatives.

Sevelamer is a nonabsorbable cationic polymer that exists in two forms as sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela). The hydrochloride formulation was used in veterinary medicine in the 90's and 00's before being removed from the U.S. market because of the acidifying effects of the hydrochloride. It can be found compounded. The alternative, sevelamer carbonate, replaced the chloride ions with bicarbonate thereby creating a dual effect of phosphate binding and bicarbonate production. Sevelamer's peak binding pH is 7 and it has less phosphate binding capacity per gram than most other phosphate binders. This reduced potency is related to a number of factors. First, sevelamer is a non-specific ion exchanger hence as it moves through the GI tract phosphate can be displaced by other anions. Second, within the duodenum sevelamer couples with bile salts limiting its ability to bind phosphorus. An additional side effect of the bile salt binding is that sevelamer can limit the absorption of lipid soluble vitamins and drugs such as vitamin D, ciprofloxacin, and mycophenolate. Overall this requires a higher dose of sevelamer to achieve similar serum phosphorus reductions in CKD patients and also higher costs hence this phosphate binder is only rarely used in veterinary patients.

Chitosan is a glucosamine polymer similar to sevelamer in that the compound contains positively charged amine moieties capable of binding phosphorus. It is one of the phosphate binders found in Epakitin along with calcium carbonate. Given that chitosan has limited amine groups (estimated to be less than ½) when compared to sevelamer, chitosan is an inferior phosphate binder at the same dosage. In addition, since chitosan is a non-specific ion exchanger, it will bind other ions throughout the gastrointestinal tract thereby further limiting its efficacy.

Hypokalemia

Hypokalemia is another common metabolic abnormality occurring in 20-30% of cats with CKD. In dogs it is less commonly clinically detected. The observed hypokalemia is secondary to reduced dietary intake and increased losses from polyuria, increased RAAS activation, and vomiting. Even moderate reductions in serum potassium can be associated with clinical signs such as lethargy, decreased appetite, muscle weakness, polyuria/polydipsia, and potentially constipation. These clinical signs are also common consequences of uremia and CKD in general making it challenging to know when a patient is suffering from hypokalemia without routinely checking serum potassium concentrations.

Potassium supplementation is recommended when dietary therapy is unable to maintain serum potassium concentrations within the normal reference range. Supplementing even when slight reductions are noted may be beneficial since there is circumstantial evidence that concurrent acidosis and hypokalemia may further reduce renal function. In addition hypokalemia is not noted until total body depletion of potassium occurs since the acidosis associated with CKD can cause cellular shifts of potassium resulting in potassium wasting not apparent on blood chemistry measurements. These observations have been further substantiated in cats where normokalemic cats with CKD have been shown to have reduced muscle concentrations of potassium. Despite these findings no studies have demonstrated that prophylactically supplementing potassium when serum concentrations are within the normal range improves survival. However many clinicians will aim to achieve serum potassium concentrations >4mg/dL in patients with CKD to prevent hypokalemia before clinical signs are apparent.

Although some potassium can be supplemented in subcutaneous fluids as potassium chloride (up to 30meq/L), in general enteral supplementation is recommended for otherwise

hemodynamically stable patients given that adverse effects are generally low. Potassium gluconate and potassium citrate are the two oral supplements used in veterinary medicine to increase serum potassium concentrations. Potassium gluconate is available as a palatable powder (Tumil-K or Renal K+) as well as a flavored gel (Renal K+) and tablet. Given this relative increased ease of administration it is a common first choice. However in patients where acidosis is also a concern potassium citrate (Polycitra K) is an excellent choice given the alkalinizing benefits of citrate. Oral formulations of potassium chloride also exist, however these are generally avoided in patients with CKD given their acidifying nature. RAAS antagonists such ACEi and ARBs also have the effect of increasing serum potassium, but are rarely used as the primary treatment of hypokalemia in patients with CKD. After initiating supplementation clinical signs including muscle weakness typically improve within 1-5 days and serum potassium concentrations should be measured every 1-2 weeks until the serum potassium concentration is achieved and clinical signs have resolved.

Metabolic acidosis

Greater than 50% of cats with advanced stage (stage IV) CKD are acidotic, however this metabolic abnormality is only present in <10% of cats with mild disease (stage II). The observed acidosis in chronic renal disease is multifactorial, but the decreased ability of the diseased kidney to secrete hydrogen ions by a myriad of mechanisms is most influential. While metabolic acidosis may have a direct effect on reducing renal function, perhaps more clinically important is how acidosis affects the patient systemically and drives catabolic processes. Problems including protein wasting, negative potassium balance, calcium loss, bone demineralization, and uremia paired with the clinical signs of muscle loss, weight loss, lethargy, weakness, and anorexia may ensue. Alkalinization therapy can reverse these and should be instituted if patients continue to have persistent bicarbonate levels below 15mEq/L despite adequate fluid balance and appropriate nutritional management. As with the other metabolic abnormalities discussed above, changing to a renal specific diet may correct mild acidosis as renal diets are neutral to slightly alkalinizing. If after a few weeks of feeding a renal diet the acidosis persists then drug therapy consisting of sodium bicarbonate or potassium citrate can be implemented, with the latter having the added effect of potassium supplementation in hypokalemic animals.

When possible the total daily dose of an alkalinizing supplement is best administered over 2 or 3 separate administrations to prevent large fluctuations in blood pH. Sodium bicarbonate is readily available and inexpensive however as a powder it is not very palatable. Compounding the powder into capsules or administering tablets is generally preferable to mixing the powder in food. Potassium citrate is a good alternative treatment since its use can have the dual effect of correcting hypokalemia. Upon initiating therapy serum bicarbonate concentrations or blood pH should be checked in 2-4 weeks and dosages adjusted as necessary. Target bicarbonate concentrations of 18-25mmol/L in dogs and 15-22mmol/L in cats are recommended with the serum concentrations checked before bicarbonate administration.