Phosphate Binders And Canine Kidney Disease

A dog's health and quality of life are severely undermined by the build-up of toxic blood phosphorus during canine kidney disease (CKD). Studies tell us that controlling how much phosphorus dogs eat becomes a priority in later stages of the condition and phosphate binders become an increasingly essential element in battling the disease. But deciding which binder to use and when to start one are not always straightforward decisions and current research is starting to question traditional advice. This article outlines the reasons for phosphate binders, explains the decision-making process and hopefully helps support conversations you will need to have with your trusted vet.

Most avid gardeners will already know that phosphorus is a key ingredient to plant life. It's added to fertilisers and plant food to enhance growth and flowering, and to boost fruit and crop production capabilities. As a mineral, phosphorus is not found freely distributed or naturally occurring on Earth. It is however found in compound form in both rock and soil. Plants extract phosphorus from the ground, and all human and animal life acquires the mineral from foods we eat.

Phosphorus is an essential ingredient of life and the second most abundant mineral in the human body. It is found mainly in the bones and dental structure of all animals and helps to support the structure of the skeleton and keep other parts of the body healthy. The kidneys regularly extract any excessive amounts of phosphorus and discharge them in urine, and this function maintains a safe phosphorus-calcium balance in the body. Unfortunately, excessive amounts of phosphorus disrupt calcium levels in the blood, and dangerous symptoms begin to develop as this process draws more and more calcium out of bones.

When damaged kidneys are unable to fulfil their role efficiently, it disrupts the essential control of phosphorus and calcium levels. These changes are responsible for some of the serious health problems seen in CKD and increase the rate of further kidney damage. If these changes remain unchecked and unstable, progressive toxaemia and devastating domino effect repercussions occur to overall health.

Why do dogs need phosphorus?

Apart from it being an essential building block for bones and teeth, phosphorus also assists in metabolising carbohydrates and fats. It also enables proteins to undertake the necessary growth and repair of cells and tissues. It is furthermore involved in a molecule being produced called ATP (adenosine triphosphate), which keeps a store of energy ready for constant use by the body. Phosphorus beneficially interacts with B vitamins, a process that assists the regulation and maintenance of heartbeats, muscle contractions, nerve signals and kidney function. In short, dogs could not survive without adequate amounts of phosphorus (see below for daily intake guidelines) – but on the other hand, excessive amounts circulating in the body without correction will lead to disastrous health consequences over time.

Are phosphate and phosphorus the same thing?

When discussing the management and treatment of canine kidney failure, owners are sometimes confused by the terms ‘phosphate’ and ‘phosphorus’.

Phosphate is a compound that’s found in its natural form in rock, but also in the ground due to intensive agriculture and the abundant application of fertilisers. Phosphate contains phosphorus. Phosphorus isn’t a stable element on its own, which is why dogs acquire phosphorus from phosphate sources. This usually means from eating meat, fish, grains and other foods (including processed and natural products). Phosphate binders make chemical changes to the phosphate compounds in food, turning the phosphorus element into an insoluble compound that cannot be absorbed into the body.

How much phosphorus is safe for my dog?

Healthy dogs will typically excrete any excessive amounts of phosphorus, which means there is no need to quantify or control the amounts taken in from a varied, nutritious and good quality diet. Dogs with progressive kidney failure that cannot excrete phosphorus are prone to developing complications that will cause a rapid worsening of the condition, as well as other associated symptoms and disorders. Vets usually suggest restricting phosphorus intake from the point of diagnosis.

Dogs in advanced kidney failure should have no more than 10 mg of phosphorus in their diet per pound of body weight per day. The National Research Council recommends dogs in early stage renal failure should have no more than 30 mg per pound of body weight per day, although 7 to 18 mg per pound is suggested as an even better goal to aim for. Owners should educate themselves about the phosphorus content of foods they give to their dogs and restrict it wherever possible. Most dog food manufacturers list the amount of phosphorus in their products. As a general guide, it is worth noting that bones, dairy products, whole fish with bones, organ meats, and egg yolks are all high in phosphorus. Some meats, poultry,

grains and vegetables are also moderately higher than their counterparts, so choose ingredients carefully when home cooking.

What problems does excessive phosphorus cause?

The parathyroid hormone (PTH) regulates both phosphorus and calcium levels in dogs. PTH works with Vitamin D on bones, the intestines and the kidneys to support a natural and healthy balance of phosphorus and calcium. When the kidneys start to fail, PTH concentrations rise while Vitamin D levels fall – and the rise in PTH alone causes many of the symptoms and ill-effects associated with chronic kidney failure (CKF). PTH increasingly draws both calcium and phosphorus from bone as the blood pH drops, causing a generalised weakness of the skeleton and a heightened risk of fractures. The apparent increase in calcium also further damages the kidneys and accelerates a complete failure of these organs. But the process is even more complicated than that.

The increase in blood phosphate levels attracts and binds with free ionised calcium in the blood stream. This binding of free calcium causes the body to have a relative hypocalcaemia event (too little calcium), which causes a stimulation of parathyroid hormone to correct this deficit. A fall in calcitriol reduces calcium absorption from the gut wall causing further relative hypocalcaemia, stimulating parathyroid hormone secretion and releasing calcium from the skeletal bones. The net effect is that calcium stays at the normal level, but it's being depleted from the skeleton, which can lead to osteodystrophy most commonly seen as "rubber jaw" in dogs.

Rubber jaw is a symptom worth checking for, as it provides vets with a warning of abnormal PTH and calcium levels, even when blood calcium seems apparently within normal range. Typically, teeth become loose, there is a softening of the lower jaw bone and dogs find it difficult to properly close their mouths. In addition, gum sores commonly occur and these prove slow to heal.

Unfortunately, high PTH is not always discovered in CKD, because it can stay high even when phosphorus levels become normalised after using an appropriate phosphate binding treatment. One solution to the higher PTH is to give low doses of calcitriol, which is a very specific form of vitamin D. Success using this method are unpredictable, but it's certainly worth trying.

A slow but constant accumulation of phosphorus in the bloodstream commonly leads to hyperparathyroidism, resulting in a much shorter lifespan. Hyperparathyroidism (actually, in CKF it is known as Secondary Hyperparathyroidism) adds to or exacerbates the symptoms of chronic kidney failure. These symptoms include increased thirst, increased urination, lack of appetite, weakness, vomiting, sluggishness, a swelling of the parathyroid glands in the neck, extreme fatigue and occasionally coma, urinary tract stones, poor body condition and progressive malnutrition. Research shows that, in humans, each 1 mg/dL of higher serum phosphorus levels coincides with a 31% increase of a first major cardiovascular event (likely due to elevated calcium that clogs arteries and tissues). There is precious little research to suggest this is exactly the same for dogs, but the mechanisms and illness progression seem ominously like-for-like.

Will reducing phosphorus in the diet solve the problem?

Most dog health and veterinary articles suggest phosphorus restriction is a priority once blood levels show a significant increase. I have also suggested this in previous articles on canine kidney failure. However, there is now evidence that proves restricting phosphorus in the diet may have only minimal advantages unless it's started extremely early. This is a cutting-edge kidney failure management conclusion from renowned professionals in the field. It is so new, it has yet to filter down into standard practice or veterinary recommendations. Strangely, it seems some veterinary authorities are resisting this news (for reasons so far unknown) and are continuing to rely on outdated and traditional treatment protocols.

While the studies and research conclusions all relate to chronic kidney failure in human patients, it is likely that the same mechanisms and outcome occur in dogs. In the 2016 study, *'Relationship of dietary phosphate intake with risk of end-stage renal disease and mortality in chronic kidney disease stages 3-5: The Modification of Diet in Renal Disease Study'*, the authors concluded *'phosphate intake is not tightly linked with serum phosphate concentrations in CKD …'*.

A 2015 study *('Contemporary management of phosphorus retention in chronic kidney disease: a review')* concluded that higher serum phosphorus (known as Hyperphosphatemia) is the most common metabolic complication of end-stage kidney disease. It also remarked that studies have found that subtle increases in serum phosphate levels, even within the normal range, are also associated with an increased risk for death in predialysis (where there is significant kidney impairment) and the non-kidney disease population.

Having read many recent research documents, it seems clear to me that damaging changes are already present long before blood results show higher than normal phosphorus levels. In her 2016 updated study report *('Chronic Kidney Disease [CKD] in Dogs & Cats: An update 2016')* Doreen M. Houston DVM, DVSc, Diplomate ACVIM, of Ontario, Canada, confirms that even as early as stage 1 CKD a phosphorus restricted diet is best started. And despite early diet intervention, a binder is best introduced within short succession if levels are not brought under good control.

What all this means is that the dietary intake of phosphorus is clearly not the main player in the damaging metabolic process, because a range of adaptive mechanisms come into play before blood levels substantially increase. These mechanisms involving parathormone (PTH), acidosis and the adverse mobilisation of calcium from bones are all involved in increasing the rate of damage.

While restriction of the mineral remains important, because it is likely to increase the potentially positive results expected from a phosphate binder, it is not going to solve the problems associated with high blood values on its own. Research has shown that vets and dog owners shouldn't wait for phosphorus blood levels to markedly rise, but instead introduce a binder as soon as the level moves into the higher range of normal or the lower range of abnormal.

But even that advice is probably not enough to prevent inevitable organ damage.

Theorists are starting to question whether serum phosphorus is as significant as many agencies involved in kidney failure treatment seem to think, as it seems there is little if any evidence that lowering phosphorus blood levels later into the disease slows the rate of deterioration or improves life expectancy. The current thinking is that it may need much earlier intervention to restrict phosphorus (which will mean much earlier renal-damage detection and CKD diagnosis), thereby enabling a longer period of serum phosphorus control. A good and effective binder will virtually eliminate phosphorus absorption … and, given what theorists and researchers in the field are saying, it is my assertion one is probably better started earlier than current convention.

What does a phosphate binder do?

There is a range of different binders and the choice of which is better depends on each dog, how the disease is progressing and what blood values are like. They all work in a similar way - some work like a sponge while others act more like a magnet drawing the phosphorus out. In essence, binders typically combine with phosphate (from ingested food) in the gastrointestinal tract to create an insoluble compound, which cannot be absorbed and is instead excreted. After starting a binder, the phosphorus-reducing process actually takes a while to reach the desired results (the average is between one and two months), so don't become disheartened at the outset. It is worth noting that binders should always be given with food – and separately (by at least an hour) from other medications and particularly antacids, as absorption efficacy is seriously undermined.

Are there any dangers in giving a phosphate binder to my dog?

There are health risks to using phosphate binders, which largely depend on the type of binder and the blood values and current symptoms of the dog. I will outline the risks of each type of binder further into this article.

It is worth noting at this stage that most binders include ingredients that are toxic. However, the rate and extent of toxicity and complications from substances such as calcium, aluminium and magnesium are relatively slow (albeit with exceptions in some dogs) and any dangers are often made redundant owing to kidney failure morbidity time-periods. In other words, a dog is far more likely to die from the kidney disease long before the phosphate binder's potential for toxicity becomes a problem.

Calcium-based binders are perhaps the exception to the rule, because if a dog's blood test shows abnormally high calcium levels, it is eminently dangerous to then introduce even more calcium by giving a calcium-based phosphate binder. Phosphorus levels must also be within normal range before prescribing this type of binder (see below), which presents a Catch-22 dilemma. Regular blood testing is an absolute necessity and offers both vets and owners the opportunity to react quickly to abnormal results and change the type of binder prescribed.

Can I use ground eggshells as a phosphate binder?

Yes, but using ground eggshells as a source of calcium carbonate is not always undertaken with enough care. There are dangers to this practice, including the potential for infection (from contaminated eggs and eggshells), hypercalcaemia (from calcium overdose) and alkalosis (an excessively alkaline condition of the body fluids or tissues).

Some owners give their kidney failure dogs' ground eggshells as a routine, without knowing the proper dosage, whether a phosphate binder is actually needed or whether calcium levels in the blood are abnormally high. Moreover, the calcium carbonate obtained from ground eggshells is not a premium calcium-based binder. Calcium acetate is better, as it has a superior phosphorus-binding ability, requiring about 40% less calcium to bind the same amount of phosphorus. This reduces the risk of hypercalcaemia occurring and avoids the potential of infection from contaminated eggs.

There is about 1 gram of elemental calcium in half a teaspoon of ground eggshells (equal to about 2,500 mg calcium carbonate), which is ordinarily a suitable daily dose for medium size dogs. I would however suggest owners do not use ground eggshells as a phosphate binder, but consult their vet about prescribing a safer and more suitable alternative.

Some owners use different sources of calcium, sometimes following veterinary advice – but not always. I have read people stating on various dog internet sites and forums they give calcium carbonate powders, regular and extra-strength Tums or similar calcium-based antacids, seaweed and other calcium supplements. While these all have their benefits and drawbacks, they are essentially carbonate forms of calcium and are best avoided when calcium blood levels are close to becoming or are abnormally high. Some of these types of supplement also contain undesired elements, such as high levels of sucrose and phosphorus.

I suppose the best advice is … know what you are giving your dog and check with your vet that it is the best there is, given current blood-test results.

When should I start my dog on a phosphate binder?

There is a lot of debate about this, but the consensus suggests a binder is best started when phosphorus blood level results climb and stay above 4.5mg/dL for more than a month despite restricting phosphorus in the diet.

In trying to prevent or at least better manage complications resulting from disease progression, it is important to restrict phosphorus in the diet once creatinine reaches 1.4 - 2.0mg/dL in blood test results. In early stage kidney disease, there is an opportunity to add calcium to the diet (at ratios of 3:1 of calcium to phosphorus) in the hope of bringing abnormal blood levels down in the short-term. Adding calcium (particularly when home-cooking for your dog) requires veterinary supervision and advice to prevent the risk of hypercalcaemia occurring.

All phosphate binders need giving with food, so they can bind with the phosphorus content of the meal ingested and work to their peak level.

Calcium to Phosphorus Ratios

While mentioning the 3:1 ratio above, it's important to emphasize that adopting such a high calcium to phosphorus ratio using food sources and supplements is not normal, should only be undertaken on a short-term basis and under the guidance and supervision of a vet. Calcium is an essential and the most abundant mineral in a dog's body, and the relationship between calcium and phosphorus is critical to overall well-being. When phosphorus increases, the canine body will take every measure possible to support a healthy ratio, even

by stealing calcium from bones and teeth – and despite the adverse health consequences of such extreme action.

It is easier to regulate phosphorus than try to deal with calcium changes, so dog owners are best advised to focus on this task in the hope of achieving effective control. The typical ratio of calcium to phosphorus in a healthy dog is somewhere between 1:1 and 2:1. As a percentage in food, a healthy dog needs around 0.5% to 0.9% calcium and 0.4% to 0.8% phosphorus. But in CKD (stage 3 or 4) the suggested phosphorus intake is 0.2% to 0.5%.

It may seem logical to try to increase calcium intake after a period of test-result deficiency, but as the inability to absorb calcium is a possible cause of the shortage (or indeed a possible cause of high serum calcium), it is much wiser to concentrate on lowering phosphorus to bring calcium under better control. Calcium levels can stay apparently normal in CKD or they can go high or low – but these changes are often related to phosphorus levels, which should persist as the management priority.

Calcium-based phosphate binders

PhosLo and Ipakitine are two of the most commonly used calcium-based phosphate binders. Reports suggest they produce varied and unpredictable results, although many vets recommend PhosLo (available only by prescription) over Ipakitine because the latter is a chitosan-based product and really little more than a nutritional supplement with less than 10% calcium carbonate content.

Calcium-based binders are losing some credibility among vets, not least because of the risks of hypercalcaemia and the demand for regular and more frequent blood testing. There are often higher cost implications to owners that choose calcium-based binders – and greater stress for dogs unhappy about visiting the vet to have blood drawn.

There is also a dilemma faced by many vets that prefer to use calcium-based binders, because unless serum phosphorus levels are already within the normal range in blood tests, there is a danger the calcium and phosphorus will combine and precipitate in tissues. If this happens, it is likely to generate urinary tract and kidney stones and exacerbate kidney failure.

Aluminium-based phosphate binders

Aluminium hydroxide is probably the most widely prescribed phosphate binder presently available. It is generally more effective and efficient than calcium carbonate, but it is also advantageously inexpensive in comparison to other binders with lower health risks. The problem with aluminium is it accumulates in the dog's body and becomes toxic. Healthy dogs excrete 95% of aluminium salts ingested through food, water and other everyday matter (being bound to transferrin and albumin intravascularly and then eliminated through the kidneys). Excess aluminium cannot be easily eliminated by impaired kidneys. Consequently, it slowly starts to accumulate in the dog's body. On the plus side of things, many studies and experts in the field suggest the levels of aluminium toxicity in dogs suffering from renal failure (and receiving aluminium-hydroxide), is probably over-stated.

In their 2008 case study, *"Aluminum Toxicity Following Administration of Aluminum-Based Phosphate Binders in 2 Dogs with Renal Failure."* (G. Segev, C. Bandt, T. Francey, and L.D.

Cowgill) the authors concluded *'… aluminium toxicity can occur in dogs with CKD that are supplemented with aluminum-based phosphate binders at dosage required to normalize serum phosphorus concentration.'* They advised any progressive decreases in MCV (red blood cell volume count) and microcytosis should be monitored in dogs treated with aluminum-based phosphate binders, as these are early indicators of aluminium overdose. At the time of the study, the authors helpfully mentioned that Deferoxamine combined with hemodialysis can effectively treat aluminum overload in dogs with CKD.

Toxicity concerns aside, there are also three other health worries over the use of aluminium-based phosphate binders.

Some routine vaccinations (the rabies vaccine, for example) use aluminium because it triggers or increases an immune response (known as an immune modulator). There has been significant research undertaken into the potential link between the vaccination sites on cats and dogs and the seemingly increased risk of sarcoma around those sites *('Origins of Injection-Site Sarcomas in Cats: The Possible Role of Chronic Inflammation—A Review'* by Kevin Woodward. 2011). Whether aluminium hydroxide acts like a foreign body carcinogen remains uncertain and unconfirmed, although some believe there's reliable evidence to the theory and several CKD dog owners have expressed concern over it. To help allay fears, it's worth noting that the World Health Organisation classifies aluminium as non-carcinogenic and it is more likely the very small risk of sarcoma at vaccination sites is not actually associated with aluminium hydroxide at all, but more associated with chronic inflammation and a genetic predisposition to this type of cancer.

The second health concern involves a dog's neurological system. The lungs, bones and central nervous system are the primary targets of aluminium. Significantly, it targets the brain and endocrine system and triggers a cascade of events leading to inflammation, neurotoxicity and disease. It's thought likely that the inflammation causes memory and learning issues in humans (possibly symptoms of slow-onset dementia), although there is very limited study facts to help confirm or deny the same process occurs in dogs.

The third health concern is constipation. Dogs taking aluminium hydroxide commonly suffer from this side-effect, which then needs treating carefully so as not to cause even more mineral and electrolyte imbalance problems.

It is interesting to note that calcium blocks some aluminium absorption, which suggests there is an advantage to using calcium-based and aluminium-based binders in combination. Very few vets attempt this remedy because it involves more intensive monitoring of blood levels to support a healthy balance of minerals and electrolytes.

Magnesium-based phosphate binders

Owing to the long-known toxicity and other health concerns of using calcium and aluminium, phosphate-binding experimentation started to look at the use of alternative magnesium compounds and lanthanum salts. Initial studies concentrated on magnesium hydroxide as a suitable compound, but these provided poor results with widespread side-effects. Research then moved to magnesium-carbonate. In 1986, 'The Lancet' published *'Substitution of Aluminium Salts by Magnesium Salts in Control of Dialysis Hyperphosphatemia'* by Richard O'Donovan et al, which proved the value of magnesium-carbonate. In its day, this was

ground-breaking research that seemingly addressed one of the biggest stumbling blocks involved in treating renal disease.

The passage of time has shown that magnesium carbonate often needs giving with calcium-carbonate to have even a moderate phosphate-binding effect, but there are also enormous and debilitating side-effect trade-offs to this approach. Reports of constant and profuse diarrhoea became common – and further studies also showed dogs had a very limited ability to excrete magnesium, causing a higher risk of toxicity likely in a shorter time-period than aluminium. Moreover, despite promising early study data, magnesium is not as good at binding with phosphorus as aluminium. As a result, magnesium compounds are very rarely used by vets as a phosphate binder today.

Sevelamer hydrochloride

In the search for a phosphate-binder that doesn't include either aluminium or calcium and therefore wouldn't cause the same issues of bone toxicity and encephalopathy (brain disorder), scientists developed a medicinal form of sevelamer hydrochloride. It's suggested this cross-linked polymeric resin binds phosphorus in a completely different way by adhering to the mucous membrane of the intestines. In turn, this slows the transit time of the compound and improves its phosphate-binding ability. During the process, it releases chloride, which means vets need to check serum chloride levels closely during treatment to prevent adverse heart, nervous system, blood oxygen and fluid imbalance effects occurring. Renagel is the leading phosphate binder containing sevelamer hydrochloride on the market.

In *'Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice'*, which is widely respected as an authoritative guide, the author Stephen P. DiBartola suggests that while sevelamer hydrochloride is a useful and promising development, there are studies that show calcium acetate is actually superior to it in controlling high serum phosphorus (hyperphosphatemia). There are also known common side effects including sometimes severe gastrointestinal issues. Another problem is it's able to bind to other bodily substances such as bile acids, vitamins (D, E, K, and folic acid) and cholesterol as well as phosphorus, which are then all excreted at the same time. This effect is often contrary to what's actually needed and can lead to other complications.

In a 2014 review of all established phosphate binders *('A comparative study of phosphate binders in patients with end-stage kidney disease undergoing hemodialysis'* by Prajapati, Galani and Shah), the authors considered sevelamer hydrochloride is as good as the others at lowering phosphorus levels but better at lowering incidences of hypercalcemia and reducing parathyroid hormone levels.

Perhaps the biggest drawback of sevelamer hydrochloride for many owners is the cost. It is a very expensive drug and often prohibitive due to that fact alone.

Lanthanum carbonate

The use of lanthanum carbonate (also free of calcium and aluminium) to bind phosphorus is a very recent development. In his work *'Lanthanum carbonate as a first-line phosphate binder'*, the specialist in nephrology Tilman Bernhard Drueke says: *'Lanthanum is a rare-earth trace metal with industrial and agricultural applications. As a therapeutic, this metal-based binder appears effective in reducing serum phosphorus, yet concerns remain about*

lanthanum accumulation in tissues during long-term oral administration. Similar to the metal aluminium, lanthanum is absorbed in the intestine and accumulates in body tissues, especially in the liver, bone, muscle, kidney, and brain. Moreover, the rate of intestinal absorption of lanthanum is enhanced in chronic renal failure.'

In theory, lanthanum should not accumulate excessively in renal failure dogs because it's excreted in bile, but Drueke's contrary concerns about absorption rates are noteworthy and the long-term implications and health risks are as yet untested and unknown. In comparison to aluminium (excreted largely by the kidneys), lanthanum is advantageously removed more through the hepatic system. Renalzin and Fosrenol are prescription drugs used for the delivery of lanthanum carbonate in animals, although these products are mostly targeted towards cats than dogs.

Myalgia (muscle pain), muscular cramping, and peripheral oedema (swelling caused by fluid accumulation) are known short-term concerns and side-effects. Just like sevelamer hydrochloride, this is also a very expensive phosphate binder and its application in the veterinary treatment of canine kidney failure is uncommon and sporadic.

Dosages of phosphate binders:

Calcium Acetate: The dose of calcium acetate is dependent on blood values. A suitable starting dose per day is 15 mg per pound of body weight when phosphorus levels in the blood are below 6.0mg/dL. The dose needs apportioning and feeding with each meal. The dose can rise to 27 mg per pound of body weight to reach phosphorus control in late stage kidney failure, and is on top of up to 1,000 mg of calcium per pound of food (needs careful calculation), contained in the food and/or given in supplements. If these doses fail to have the desired effect or if calcium blood levels rise to abnormal levels, talk to your vet about switching to another binder.

Calcium Carbonate: Like calcium acetate, the dose of calcium carbonate is dependent on blood values. A suitable starting dose per day is 15 mg per pound of body weight when phosphorus levels in the blood are below 6.0mg/dL. The dose needs apportioning and feeding with each meal. The dose can rise to 45 mg per pound of body weight to achieve phosphorus control in late stage kidney failure, and is in addition to up to 1,000 mg of calcium per pound of food (needs careful calculation), contained in the food and/or given in supplements. If these doses fail to have the desired effect or if calcium blood levels rise to abnormal levels, talk to your vet about switching to another binder.

Aluminium Hydroxide: Use aluminium hydroxide gel powder and mix it into food, to get the best results. The starting dose is 15 mg daily per pound of body weight when phosphorus levels in the blood are below 6.0mg/dL. If phosphorus levels rise to 8.0mg/dL, the amount of aluminium hydroxide should progressively but cautiously increase to an upper-limit of 100 mg per pound of body weight (Larry Nagode DVM Ph.D. of The Ohio State University Veterinary College). As all phosphate binders take some time to have an effect, dosages are best reassessed and increased when necessary at monthly intervals. Aluminium hydroxide is known to start reducing serum phosphorus after about 10 to 14 days, so the first post-binder blood check is best undertaken at this stage.

Magnesium Carbonate: When given as Pronefra the dosage is 1 ml per 5 kg of a dog's weight given twice daily with meals. This particular binder product entered the market in

2014 and combines magnesium carbonate with calcium carbonate. Studies report moderate success in reducing phosphorus and creatinine in cats with kidney disease, but similar studies in dogs have not been conducted, so the success of its use in canine kidney disease is uncertain.

Sevelamer hydrochloride: Recommendations on dosing for dogs could not be found at the time of writing. Vets prescribing it need to calculate a therapeutic dose from human recommendations (as outlined below). Renagel is a pharmaceutical product for delivering sevelamer hydrochloride into the human body.

The recommended starting dose of sevelamer hydrochloride is 2.4 g, 3.6 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renagel requires administering three times per day with meals. Serum phosphate levels need monitoring closely and the dose of sevelamer hydrochloride titrated by 0.4 g or 0.8 g three times per day (1.2 g/day or 2.4 g/day) increments with the goal of lowering serum phosphate to 1.76 mmol/L (5.5mg/dl) or less. Serum phosphate requires testing every two to three weeks until it becomes stable and regularly after that.

Lanthanum carbonate: In a study review of canine toxicology using lanthanum carbonate hydrate (Fosrenol) conducted in 2002, the proposed starting dose of 750 mg per day taken proportionately with meals proved safe and effective. The same study suggests cautious upward titration of the dose to an upper limit of 3,000 mg per day or until serum phosphorus levels fall. The researchers found notable tissue accumulation of lanthanum occurred at 2,000 mg per day at the end of a 52-week trial, and I would interpret that to mean that less than 2,000 mg a day is a better and slightly safer upper limit. There were no specific or common toxic symptoms identified in the study – and after stopping treatment using the drug, serum lanthanum levels slowly reduced.

New research into alternative phosphate binders

There is a huge amount of scientific research happening all over the world trying to find and develop new phosphate-binding alternatives. While this research is generally all human-centred, there are usually consequential applications in the veterinary treatment of kidney failure.

One of the most promising avenues explored in recent years was the PEACH pivotal study of PT20 by scientists in Cambridge in the United Kingdom. Exclusively licensed by Phosphate Therapeutics, this is a novel phosphate binder based on proprietary ‘Interstitial Mineral Hydroxide’ technology using adipate-doped iron oxide at the core of the product, thereby allowing PT20 to act as a very high-capacity ‘phosphate sponge’.

Dr Geoffrey Block, MD, the study’s lead Investigator commented in 2015: *‘The highly positive results of this first pivotal study of PT20 provide a very encouraging start to the clinical pathway of this exciting product. The management of end stage renal disease inherently carries a large treatment burden for the patient and having an iron-based phosphate binder with such an apparently positive safety and efficacy profile at this stage of development suggests the product could be of high clinical value to both doctors and patients in the future.’*

The March 2016 edition of Kidney News reported that the first absorbable iron-based phosphate binder, Auryxia (ferric citrate), is now available for humans as a result of this exciting research. Whether it has any positive canine applications depends on further veterinary developments, clinical trials and testing in the future.

There is another and completely different avenue of research being conducted into the role that saliva might play in phosphorus absorption. This began because it was found that phosphorus levels in saliva were ominously higher in human kidney failure patients – and, significantly, it was higher in saliva even before an abnormal rise occurred in blood phosphorus. Early Italian studies (2009) suggested a chitosan-loaded chewing-gum was successful in reducing blood levels, but the results of this study were found to have flaws and could not be replicated by other researchers.

In 2016, scientists discovered that using the chewing-gum approach combined with a traditional phosphate binder accentuates the effects of the binder and efficiently contributes to lower phosphatemia in human CKD patients *('Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide'* by Cernaro V, Santoro D, Lacquaniti A, Costantino G, Visconti L, Buemi A, Buemi M). While the chewing-gum approach may not directly benefit dogs with the disease, it could lead to new and more suitable veterinary products being introduced in due course.

Although not connected to phosphate binders, there is another fascinating study looking into the extraordinary rejuvenating quality of American black bear kidneys, which on the face of it seems a fairly unique physiological occurrence in the mammalian world.

"Black bears go into hibernation in the fall with healthy kidneys," says Ron Korstanje, PhD, a researcher at the Jackson Laboratory in Maine, in an article on the Jackson Laboratory website. *"They don't urinate during hibernation, and by the time spring arrives, their kidneys are damaged and have lost most of their function."* At that point, the bears' kidneys seem to regenerate themselves, returning to normal function during the spring and summer. *"How does that happen?"* Korstanje asks. *"And if we figure that out, can we come up with treatments that can prevent or reverse kidney damage?"*

While these and many more studies and research programs are occurring all over the world, we are perhaps sometimes frustrated that we often seem to take two steps forward and one backward in developing new and creative treatments for canine kidney disease. And while that is perhaps true, at least we are moving slowly forward in the search for effective treatments.

In Conclusion

While trying to work out the best phosphate binder to treat a dog with chronic kidney failure, I have found there are far too many variables to give a definitive response. My choice would probably be sevelamer hydrochloride, despite it being extremely expensive and having unknown long-term consequences. The biggest hurdle to overcome in using sevelamer hydrochloride is there are no dosing recommendations available for dogs, which means vets need to calculate safe and effective quantities from reports into human treatment.

The next best choice is probably aluminium hydroxide combined with a low dose of calcium acetate, bearing in mind this dual treatment approach involves frequent and costly blood-

testing to make sure mineral and electrolyte balances and other associated blood values remain stable.

If cutting-edge theoretical conclusions prove correct, it is clearly important to start a phosphate binder as early as possible despite the potential toxicology and mineral/electrolyte complication risks of longer term treatment.

It is important to mention that I am not a vet. Owners should discuss the options available with their own vet who, armed with a comprehensive set of urine and blood test results, will recommend the best and most appropriate phosphate binder based on a case-for-case basis and taking into consideration any pertinent other health issues a dog might have.