Niacinamide to Lower Phosphorus in CKD Cats

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Vitamin B3 in the form of niacinamide is proving to be a safe, non-toxic method of lower phosphorus levels. It is not a binder like aluminum or calcium, it blocks a portion of phosphorus uptake. It does not cause constipation, nor does it have potentially toxic side-effects.

First: A note of caution. Please be mindful.

There are no studies of the use of niacinamide in cats to control phosphorus, this is uncharted territory. To our knowledge, the initial fears of low platelets (read below) has not been borne out in cats. However, a side effect in cats not reported in these human studies (see below) is elevated liver values. ***Close monitoring of phosphorus values is important in initial use*** as there are no dosage guidelines for cats. We do not know how many are using niacinamde to control phosphorus because of this article or the sale of niacinamide on a pet wellness / medication site, but over the four years this article has been up, we are only aware of four cats that developed elevated liver values. Thus, if at any point during use of niacinamide for phosphorus control elevated liver values are seen in blood work, stop its use. Once the niacinamide is stopped, it has been reported to us in these few cases that liver values return to normal in rather short order. (We don't have timelines). But kitties feel better quite quickly. Use of milk thistle or Denamarin for Cats can aid the healing process.

Niacinamide and Phosphorus Binders

There are two primary phosphorus binders used in cats: Aluminum hydroxide ("ALOH") and Epakitin (calcium carbonate and chitosan). Calcium as a binder cannot be used if calcitriol is being used to prevent secondary hyperparathyroidism and calcium has been known to cause hypercalcemia in CKD cats. ALOH binds phosphorus more effectively than calcium carbonate, which is why it is the typical binder of choice in feline CKD. The most common side-effect of both binders is constipation, though, as noted, calcium carbonate can lead to hypercalcemia, and long-term use of aluminum in cats has not been evaluated (there is no known safe dose of aluminum in humans, and aluminum can be retained in the body, particularly in the bones). Aluminum is also known to cause muscle weakness and microcytic anemia, and we may not be able to distinguish these impacts of the binder from the complications of

the kidney disease in our cats. It has come to our attention that there is a potential safe, effective alternative method for phosphorus control: a specific form of vitamin B3 (Niacin / Nicotinic Acid) called niacinamide (or nicotinamide). Many vets are familiar with niacinamide for its use (long term) in treating a nail fungus common in dogs and are of the opinion, based on their experiences, that it is quite safe, having only occasionally observed gastrointestinal problems in the form of nausea in dogs using it at "high doses" – and as for humans as discussed in the studies (list of those below), a dose reduction typically resolves that problem.

To date, from 2005 – 2017 there have been ten studies of niacinamide in CKD / CRF (in humans) published in peer review journals. A comprehensive list of those studies (and review pieces) is included below. Please note, some of the studies use niacin, some use niacinamide. Niacinamide is notable for having fewer side-effects (the most well-known side-effect of niacin, flushing, is not experienced when using niacinamide). Doses of niacinamide in the studies for humans typically range from low (for a human) doses of 500mg/day to high, 2,000mg/day, and in all but one study, the doses are split into half given twice a day. Notably, each study has demonstrated a dose-dependent reduction in phosphorus.

People who have used niacinamide for phosphorus control in their cats are seeing rapid reductions in phosphorus levels. Niacinamide is not a binder, it works by blocking the uptake of phosphorus. In the studies, not only does it **not** raise calcium or PTH levels, it appears to have a role in managing them by lowering both phosphorus and a growth hormone (FGF23) that impacts this process (Rao et al 2014. *Effect of Niacin on FGF23 Concentration in Chronic Kidney Disease*).

In feline CKD groups, the question of a potential relationship between niacinamide and thrombocytopenia (low platelets) is often raised in such a way it scares many people away from trying this non-toxic, effective method of phosphorus control. Please note this important information:

In the 10 published studies that encompass thousands of participants, thrombocytopenia was observed in just one study in just four people (Lenglet 2017). Important to note is:

1) This study used the highest dose of niacinamide (2,000mg)
2) Unlike ***all*** the other studies, this dose was given once a day, not split into half and given twice a day. The authors noted that splitting the dose into half (1,000mg) given twice a day might have resulted in no one developing the low platelets, and, importantly
3) **the problem corrected when they stopped the niacinamide, and platelets "quickly" returned to normal.**

Please also note, a 10% reduction of platelets did occur in 2008 Cheng et al, *A Randomized Double-Blind Placebo Controlled Trial of Niacinamide for Reduction of Phosphorus in Hemodialysis Patients*. **This was seen in both the group treated with niacinamide and the placebo group. This had no clinical relevance and no one had to abandon the study for it.** The study concluded it was a safe phosphorus control option (and we note in this study, people were on 1,500mg for eight weeks). Of note, thrombocytopenia is a common problem in humans with CKD on dialysis (Dorgalaleh et al 2013, *Anemia and Thrombocytopenia in Acute and Chronic Renal Failure*). Between us, Carolina and Laurie, we have had five cats on niacinamide. None of our cats have lower platelets. Several have higher counts, and in Carolina's cat, platelets have steadily risen over the two years he's been on it.

In our opinion, the fear of low platelets from use of niacinamide is dramatically overstated, especially as stopping use or lowering the dose of niacinamide resolves the problem IF it even arises. Any change is

not permanent and quickly resolves (as per the observation of the study authors).

As mentioned in the first section of this article on page 1, elevated liver values in four cats in five years have been reported and this should be monitored. And as observed with low platelets in humans, stopping the use of niacinamide in cats resolved the problem of elevated liver enzymes and related inappetence.

Initial Dose for Cats with Elevated Phosphorus

First: please give niacinamide with food. It is always best to administer vitamins with food to avoid digestive upset. As with everything (especially B vitamins), some cats will eat it in food, some will not. But niacinamide should be given at or near meal time. It can be pilled (put it in a capsule), fed as a treat in a bit of food or baby food, or syringed by mixing with something, like a bit of food, tuna juice or baby food (as examples), whatever method is easiest for you to get it into your cat.

Definition of elevated: phosphorus higher than 6 mg/dL (USA) or 1.9 mmol/L (international). This is not defined in terms of lab normals, but are the cut-off points for the use of calcitriol. These levels are generally understood to be levels in CKD cats where something should be used to bring down the level of phosphorus in the bloodstream.

The recommended dose of niacinamide for cats is found on VIN (Veterinary Information Network) and posted by Dr. Lester Mandelker (an expert in veterinary pharmacology). The recommended dose for cats is 250mg of niacinamide twice per day. This has been found to result in RAPID drops of phosphorus and should only be used as a temporary dose and thus blood levels of phosphorus must be monitored. This dose has its use, but again, requires close monitoring (for instance, recheck blood work after one week to 10 days at most). Once phosphorus is at a healthy target, a lower dose of niacinamide to maintain the phosphorus level your vet feels is best for your cat is warranted.

If phosphorus is significantly elevated, niacinamide **can** be added to the phosphorus control regimen and used alongside ALOH (aluminum). This is how it was used in the human clinical trials.

Maintenance Dose of Niacinamide for Cats

Once you've brought down phosphorus levels to the target you set with your vet (we target around 4 mg/DL (1.3 mmol/L)), it has been our observation that a lower maintenance dose can be used to keep it there. What that lower twice-per-day dosing should be can vary:

1) niacinamide works in the intestines to block uptake of a portion of the consumed phosphorus, which portion can range from 20% - 40% and
2) the amount of phosphorus in the diet varies. Some feed low protein diets, some feed higher protein diets, some feed phosphorus controlled diets, etc.

We do not feed or recommend a low protein diet as senior cats need a higher protein diet to prevent muscle wasting. This is also discussed by Dr. Norsworthy in *Why Feline Kidney Insufficiency is Still Tricky to Treat*: " 'The low-protein diet really hasn't done the good that we thought it was doing,' Norsworthy said, adding that its benefits to kidney function "are minimal to nil" and that many older cats on a low-

protein diet will begin to lose muscle and get thin." Finally, the work of Finco et al in 1998 found that protein has no impact on progression of kidney damage.

With a typical raw or home cooked diet free of carbs (using a bone replacement like eggshell or calcium carbonate), we find the twice-a-day dose of niacinamide ranges from 50mg to 125mg, where just 50mg to 75mg is typical.

Brands we use are Jarrow (capsules), Nature's Plus (tablets), Pure Encapsulations and Bulk Supplements (pure powders). Any brand you like will work, all that matters is the once daily or twice-daily dose, so do make sure to pay attention to the label information on the back of any product you purchase for its specific dose and thus how to portion it into the dose you want to provide your cat.

Monitoring

If your cat's phosphorus is elevated above 6 mg/dL (USA) or 1.9 mmol/L (international) as discussed above, and you provide 250mg of niacinamide 2x per day, it is best to retest in one week to 10 days. In one of Laurie's cats, 250mg twice a day brought phosphorus down from 8.7 to 6.9 in one week.

If your cat's phosphorus is at or slightly lower than the 6mg/dL (1.9mmol/L), you can use 250mg 2x per day, but as close monitoring can be stressful on the cat and expensive, lower doses can obviously be employed and given over a longer period of time, for instance 125mg 2x a day brings down phosphorus much more slowly.

Thus, if your cat's phosphorus is near 5mg/dL (1.6129mmol/L), a maintenance dose of niacinamide (100mg – 125mg twice per day) should slowly bring down phosphorus to the target. Laurie did this in one of her cats, but please note it took **three months** to bring phosphorus down from 5.2 mg/dL (1.6774mmol/L) to near 4.0mg/DL (1.3mmol/L). It would be more efficient to use the 250mg 2x/day for a week, lower to 100mg (or 125mg) 2x/day and retest after a month. If on target, lower again to 50mg or 75mg 2x/day and again, retest after a month to ensure this is the correct amount for your cat and phosphorus is controlled.

As already discussed, there are no studies to provide guidance. We have only the one suggestion from a vet, and that was a very aggressive amount of niacinamide. Thus we have to adjust doses based on the blood work of OUR cats and the diet we feed.

We recommend discussing the use of niacinamide and monitoring phosphorus levels with your vet.

You can download to print or email the PDF file if your vet would like to review this information and the existing research.

Next: Information on Niacinamde and the research conducted in humans using it for phosphorus control.

Niacin (nicotinic acid), is vitamin B3. Niacin, niacinamide / nicotinamide have been studied in the prevention of hyperphosphatemia. Niacin is sold in a prescription format to lower cholesterol in humans. It has some unwanted side-effects, including flushing and lowered platelets. **These side-effects are not observed with the bioactive form of niacin, which is niacinamide (also known as nicotinamide).** Niacinamide / nicotinamide are synonymous. The name reflects the bioactive form of niacin, an "amide" of niacin.

Differences between Niacin / Niacinamide: https://vitanetonline.com/forums/1/Thread/2210

Feeding the Kidney Patient: The Low Protein Diet Myth. Article by Will Falconer, DVM. An important read. This article contains the VIN information on niacinamide dosing in cats and dogs.

The Research

Please note, doses for humans used in these studies varied from 500mg/day to 2,000mg/day. Some studies used niacin while some used niacinamide. These are all human-based studies / review pieces.

2005 Eto et al. *Nicotinamide prevents the development of hyperphosphataemia by suppressing intestinal sodium-dependent phosphate transporter in rats with adenine-induced renal failure*. https://academic.oup.com/ndt/article/20/7/1378/1911890
Conclusion: Nicotinamide inhibited intestinal Pi absorption in a rat model of CRF, at least in part by inhibiting the expression of NaPi-2b, and appeared to protect against the deterioration of renal function.

2008 discussion on niacin and niacinamide treating hyperphosphatemia: https://www.medscape.com/viewarticle/583485#vp_1
"Phosphorus is increased in most patients undergoing dialysis, and phosphorus control usually requires dietary restrictions and the use of several phosphate binder pills. Binders must be taken with each meal to create insoluble phosphate complexes, which may cause constipation, and the large pill burden can be both inconvenient and quite expensive. For these reasons, inhibition of intestinal transport of phosphorus has been an appealing alternative. In theory, inhibition of cellular uptake of phosphorus would decrease intestinal absorption and reduce phosphorus accumulation in patients with kidney disease. In vitro studies have shown that niacinamide decreases phosphate uptake, offering the possibility that niacinamide and niacin might be effective agents for phosphorus control.

Recent human clinical trials studies have shown that niacinamide and niacin inhibit intestinal transport of phosphorus and achieve clinically significant reductions in serum phosphate in patients undergoing dialysis."

The 2008 Cheng et al study referenced in the above discussion:
https://www.researchgate.net/publication/5468066_A_Randomized_Double-Blind_Placebo-Controlled_Trial_of_Niacinamide_for_Reduction_of_Phosphorus_in_Hemodialysis_Patients
"A concurrent fall in calcium-phosphorus product was seen with niacinamide, whereas serum calcium, intact parathyroid hormone, uric acid, platelet, triglyceride, LDL, and total cholesterol levels remained stable in both arms. Serum HDL levels rose with niacinamide (50 to 61 mg/dl) but not with placebo."

2010 Maccubbin - Niacin impact on patients without kidney disease:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2849700/

"Conclusions: We have provided definitive evidence that once-daily ERN-L treatment causes a sustained 0.13-mmol/L (0.4-mg/dl) reduction in serum phosphorus concentrations, approximately 10% from baseline, which is unaffected by estimated GFR ranging from 30 to ≥90 ml/min per 1.73 m2 (i.e., stages 1 through 3 chronic kidney disease)."
Note: ERN-L is the prescription form of niacin used to lower cholesterol in humans

2010 Ahmed review piece. *Niacin as a potential treatment for dyslipidemia and hyperphosphatemia in renal failure: the need for clinical trials*
http://www.tandfonline.com/doi/full/10.3109/08860221003753323
"Interestingly, recent experimental and clinical studies suggest the potential benefit of niacin as a treatment of dyslipidemia and high plasma phosphate associated with chronic kidney disease (CKD). Both dyslipidemia and high serum phosphate levels are shown to be associated with higher cardiovascular mortality. Furthermore, niacin administration improves renal tissue lipid metabolism, renal function and structure, hypertension, proteinuria, and histological tubulointerstitial injury."

2011 Vasantha et al. *Safety and efficacy of nicotinamide in the management of hyperphosphatemia in patients on hemodialysis*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3193667/
"Nicotinamide is safe, cheap and effective in controlling serum phosphorus, Ca × P product and alkaline phosphatase levels in patients on maintenance HD."

2012 Edalat-Nejad *The Effect of niacin on serum phosphorus levels in dialysis patients*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3459519/
"Our study suggests that niacin should be considered as adjunctive therapy for patients with hyperphosphatemia despite management with phosphate binders. The modest increase in HDL values may be another beneficial effect of this treatment."

2012 Kang et al. *Effects of low-dose niacin on dyslipidemia and serum phosphorus in patients with chronic kidney disease* https://www.sciencedirect.com/science/article/pii/S2211913212007693
"Low-dose niacin had a low frequency of adverse effects and also improved dyslipidemia, lowered serum phosphorus level, and increased GFR in patients with CKD."

2013 Lenglet. *Use of Nicotinamide to Treat Hyperphosphatemia in Dialysis Patients*
https://link.springer.com/article/10.1007/s40268-013-0024-6
This is a review piece that discusses the mechanism of action in detail.

2014 Rao. *Effect of Niacin on FGF23 Concentration in Chronic Kidney Disease.*
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101884/
"In this ancillary study of hyperlipidemic patients with eGFR 30–74ml/min/1.73m2), extended release niacin alone, but not in combination with laropiprant, lowered FGF23 and PTH concentrations. If confirmed, niacin may provide a novel strategy to decrease phosphorus, FGF23, and PTH concentrations in patients with CKD."

An article about the 2016 study by Zahed et al:
http://www.renalandurologynews.com/hyperphosphatemia/low-dose-niacin-helps-lower-phosphorus-levels/article/510015/
"The low-dose niacin group experienced notable phosphorus reduction over 12 weeks, according to results published in the Indian Journal of Nephrology. Average phosphorus level decreased from 6.7 mg/dL by week 4 to 5.8 mg/dL by week 8 to 4.4 mg/dL by week 12. The placebo group, by comparison,

saw a rise in phosphorus level from 6.5 mg/dL to 7.2 mg/dL by the end of week 12.

Consistent with previous research, niacin treatment also increased high density lipoprotein (HDL) levels from 45.0 to 47.2. None of the participants had received statins or resins.

Previous studies have shown that niacinamide and niacin can reduce serum phosphate levels in dialysis patients. The current findings complement these studies."

The study: 2016 Zahed. *Effect of low dose nicotinic acid on hyperphosphatemia in patients with end stage renal disease*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4964682/
"We conclude that niacin (100 mg/day) decreased phosphorus serum level and increased HDL serum level in patients on dialysis."

2017 Lenglet et al. *Efficacy and safety of nicotinamide in haemodialysis patients: the NICOREN study*. https://www.ncbi.nlm.nih.gov/pubmed/27190329
"Both drugs are equally effective in lowering serum phosphorus, but patients' tolerance of NAM was largely inferior to that of SEV. Extremely high 2PY levels may contribute to NAM's side effects." We note: this conclusion is interesting, because they provide a list / comparison of the side-effects noted with each binder. The incidence of side-effects directly related to niacinamide appears to be no different than those in the sevelamer group. Refer to P 875.

On niacin in our pets, general information:
https://www.dsm.com/markets/anh/en_US/Compendium/companion_animals/niacin.html