Niacinamide to Lower Phosphorus in CKD Cats

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There are two primary proven phosphorus binders used in cats: Aluminum hydroxide ("ALOH") and Epakitin (calcium carbonate and chitosan (which cannot be used if calcitriol is employed to prevent secondary hyperparathyroidism)). 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 either binder is constipation, though 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 in addition to feeding reduced-phosphorus food, there is a potential safe, effective alternative method for phosphorus control: a 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 seen only gastrointestinal problems in pets using it (and as seen in the studies in humans, a dose reduction typically resolves that problem).

There have been a number of published studies in humans, and a comprehensive list of those studies and reviews is included here. 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 range from low (for a human) doses of 500mg/day to high, 2,000mg/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 a growth hormone (FGF23) that impacts this process (Rao et al 2014. *Effect of Niacin on FGF23 Concentration in Chronic Kidney Disease*).

In a number of discussions on the use of niacinamide for phosphorus control, the question of a

potential relationship between niacinamide and thrombocytopenia is often raised. Thrombocytopenia was a side-effect in ONE study (2017 Lenglet). This study used the highest dose of niacinamide (2,000mg), and the problem corrected when niacinamide was stopped. The study authors noted that the problem may not have developed if people had been instructed to split the dose of niacinamide in half, and take each portion twice a day (as in most of the other studies) rather than the large dose once a day. 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*. We note 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 counts higher than when they started. To our knowledge, low platelets have not been observed in any cats using niacinamide.

The only currently recommended dose for cats is on VIN (Veterinary Information Network). It is posted by a respected veterinarian. The recommended dose is 250mg of niacinamide for our cats twice a day. (It does not need to be given with food, but can be). People who have given this dose to their cats have seen rapid drops in phosphorus levels even when the starting point was double-digit. It will be best to monitor levels closely while lowering phosphorus quickly, and then changing to a lower dose of niacinamide to maintain the phosphorus level your vet feels is best for your cat. If phosphorus is significantly elevated, niacinamide can be added to the phosphorus control regimen and used alongside ALOH as it has been in the human clinical trials. That said, if levels are already consistent with IRIS staging-related targets, based on our experiences using niacinamide, blood work should be monitored at two weeks after starting the binder. If elevated to over 6 mg/dl (USA) or over 1.9 mmol/L (international), if using 250mg of niacinamide twice a day, it is probably be best to recheck phosphorus values in 3 weeks to a month. A maintenance dose of 75mg (if purchasing powder, 1/32nd flat teaspoon (the "smidgen" in the mini teaspoon sets)) twice a day appears to be effective, though what is best for your cat will vary a bit depending on the phosphorus content of the diet. Being the "first adopters," if interested in using this non-toxic, non-constipating alternative with your kitty, we suggested you discuss its use and a testing schedule with your vet. You can't go wrong using smaller doses. 100mg twice a day will bring phosphorus down slowly but steadily. Laurie used 100mg for one of her cats twice a day. Her phosphorus very slowly fell from 5.2 to 3.9 over three months in a non-protein restricted diet. Double that dose achieved the same change in a month in a different cat. 250mg twice a day brought a third cat from 8.7 to 6.9 in one week. A good rule of thumb? Do not exceed 250mg 2x a day. Consider that a high dose. With that in mind, the higher your starting dose, the more frequently you should recheck blood work.

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

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

The Falconer piece that has the VIN info on dose for cats (though your vet can easily find the original recommendation on VIN): https://vitalanimal.com/low-protein-diet-myths/

The Research:
Please note, doses of Niacinamide / Nicotinamide varied in these studies from 500mg/day to 2,000mg/day. 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.
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> 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 general: https://www.dsm.com/markets/anh/en_US/Compendium/companion_animals/niacin.html