MEDICAL MANAGEMENT OF CHRONIC KIDNEY DISEASE IN CATS

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SUMMARY

Despite recent technological advances in dialysis and transplantation, conservative medical management remains the most practical and accessible approach to the treatment of chronic kidney disease (CKD) for most cat owners and veterinarians. When initially presented, many cats with CKD are moderately to severely dehydrated and require rehydration over 24-96 hours to resolve pre-renal azotemia and correct existing acid-base and electrolyte disturbances. Medical management is begun only after rehydration has been completed.

NUTRITIONAL CONSIDERATONS

Owners must understand the importance of providing the cat access to fresh water at all times. Cats with CKD cannot concentrate their urine and rapidly become dehydrated without ready access to water. Fresh water should always be available and consumption of liquids should be encouraged. Cats should consume a minimum of 20% of their daily calories (approximately 4 g/kg/day when consuming 70 kcal/kg/day) as high quality protein. These guidelines represent absolute minimum values and do not allow for maintenance of body nitrogen reserves. Most commercially available cat foods modified for renal failure provide additional protein, and such diets also are phosphorus and sodium restricted. Protein restriction should be considered when moderate azotemia persists in the well-hydrated state. The clinician should strike a balance between reducing protein intake and the cat's willingness to eat. Maintenance of stable body weight and serum albumin concentration suggests adequate intake of calories and protein whereas progressive declines in body weight and serum albumin concentration suggest malnutrition or progression of disease and are indications to increase the amount of protein fed. If possible, the cat should be acclimated to the new diet while its appetite is still reasonably good and the transition should be made gradually over several weeks. Recent studies have shown a beneficial survival effect of feeding commercially-available modified renal diets to cats with CKD. Cats with CKD fed a protein-restricted, phosphorus-restricted veterinary diet survived a median of 633 days compared to 264 days for cats fed a conventional diet. In a retrospective study of cats with CKD fed several different commercially available modified diets, median survival time was 16 months in cats fed the modified diets compared to 7 months in cats fed conventional diets, and the diet associated with the longest survival time (23 months) had a relatively high content of eicosapentaneoic acid. Cats with CKD are less flexible in adjusting to changes in dietary sodium load, and many commercial pet foods provide more sodium than needed (often about 1%). Commercial products marketed for cats with CKD provide about 0.2-0.3% sodium. Gradually switching an animal to a renal diet will result in gradual sodium restriction. Excessive sodium restriction in cats with reduced renal mass may result in reduced glomerular filtration rate, inappropriate kaliuresis, and activation of the renin-angiotensin-aldosterone system without beneficial effect on systemic blood pressure, and the use of sodium-restricted diets may warrant reconsideration. Water soluble vitamins should be supplied in the diet of cats with CKD because the ability of the diseased kidney to conserve these vitamins is not known.

PHOSPHORUS BINDERS

Early phosphorus restriction in CKD has been shown in dogs and cats to blunt or reverse renal secondary hyperparathyroidism. When CKD is diagnosed, phosphorus restriction is initiated by feeding a low-phosphorus, low-protein diet. If necessary, oral phosphorus-binding agents can be added to the treatment regimen for additional control of hyperparathyroidism. In a study of cats with naturally-occurring CKD, renal secondary hyperparathyroidism was successfully managed by dietary restriction of phosphorus, and only one-third of the

cats also required treatment with phosphorus binders. Phosphorus-binding agents should be given with meals or within 2 hours of feeding to maximize their binding of dietary phosphorus. Oral phosphorus binders include aluminum hydroxide, calcium carbonate, calcium acetate, sevelamer HCl and lanthanum carbonate. The starting dosage of aluminum and calcium containing phosphorus binders is approximately 90 mg/kg/day, and the dosage should be adjusted by periodic evaluation of the serum phosphorus concentration in a blood sample obtained after a 12-hour fast. Animals should be monitored for development of hypercalcemia whenever phosphorus binders containing calcium are used, especially if calcitriol is being administered concurrently. Sevelamer HCl is a phosphorus binder that does not contain aluminum or calcium. Due to its potential for binding vitamins in the gastrointestinal tract, vitamin supplementation is recommended during treatment with sevelamer. Lanthanum carbonate is safe and well tolerated in cats up to a dosage of 1 g/kg/day. In normal cats, at this dosage it decreased phosphorus digestibility by 22% and shifted phosphorus excretion from the urine to the feces. A nutritional supplement called Epakitin® contains chitosan and calcium carbonate and has been recommended for use as a phosphorus binder in cats. At the recommended dosage (1 g per 5 kg body weight q12h) this product supplies 20 mg/kg of calcium carbonate q12h. Thus, in addition to the potential adsorbent effect of chitosan on urea and ammonia, the calcium carbonate contributes a phosphorus-binding effect.

H2 RECEPTOR BLOCKING DRUGS AND ANTI-EMETICS

Plasma gastrin concentrations are abnormally high in cats with CKD. The degree of hypergastrinemia tends to correlate with the severity of CKD. In a recent study of cats with CKD, however, histopathology of the stomach showed only fibrosis and mineralization and not gastric ulceration or fibrinoid vascular changes. Thus the use of H2 receptor blocking drugs in CKD cats may not be helpful in the management of vomiting and anorexia previously attributed to uremic gastroenteritis. Famotidine however has been used commonly in cats with CKD at a dosage of 1 mg/kg/day orally. The 5-HT_3 receptor antagonist mirtazapine increased appetite, activity, and body weight and decreased vomiting in CKD cats when used at a dose of 1.88 mg ($1/8^{th}$ of a 15 mg tablet) orally once every 48 hours. Adverse effects were not observed except for an increase in alanine aminotransferase activity in one treated cat that resolved with discontinuation of treatment. Thus, vomiting in CKD cats may be centrally-mediated and mirtazapine may be helpful in its management.

ALKALI REPLACEMENT

The metabolic acidosis of CKD often is well-compensated, and routine treatment may not be indicated. Recent studies of cats with CKD have shown that evidence of metabolic acidosis usually is not present until CKD is advanced. It was found in about half of the advanced cases, in only 15% of moderate cases, and in none of the mild cases. If metabolic acidosis is severe (bicarbonate $\leq$ 12 mEq/L), $NaHCO_3$ may be added to the treatment regimen but such use does impose an additional sodium load. Potassium gluconate and potassium citrate are alternative sources of base that provide potassium and do not pose the problem of additional sodium.

POTASSIUM SUPPLEMENTATION

Hypokalemia in cats with CKD may impair renal function, and in one study feeding of a high-protein, low-potassium, acidifying diet was associated with development of lymphoplasmacytic interstitial nephritis in previously normal cats. Approximately 20 to 30% of CKD cats are hypokalemic at initial presentation. Correction of hypokalemia is accomplished using orally administered potassium gluconate or potassium citrate. The dosage required often is about 2 to 4 mEq per day of potassium. Muscle potassium content may be decreased in normokalemic CKD cats, but glomerular filtration rate did not improve after 6 months of potassium gluconate supplementation in affected cats in one study. Whether or not potassium supplementation is indicated in normokalemic cats with CKD is unclear.

ANABOLIC STEROIDS

The use of anabolic steroids (e.g., stanozolol) in CKD is empirical and their efficacy remains to be documented. The margin of safety for the commonly used anabolic steroid, stanozolol in cats is narrower than in dogs and it may result in hepatotoxicity characterized by hepatic lipidosis and cholestasis with minimal hepatocellular necrosis. Thus, use of anabolic steroids in cats with CKD is not recommended.

MANAGEMENT OF HYPERTENSION

The prevalence of hypertension in cats with CKD is variable and ranges from approximately 30 to 75% of affected patients. The prevalence of hypertension may be higher in animals with glomerular disease. Cats especially are prone to "white coat artifact" making it difficult to determine if a given cat is truly hypertensive. In clinical practice, systolic blood pressure usually is measured by Doppler technique. Sufficient time for acclimation should be allowed, and several sequential measurements should be made to assess the animal's blood pressure. Averaging sequential readings improves reliability. Cats with systolic blood pressure readings consistently above 170 mm Hg or those with abnormally high blood pressure readings that also have fundic lesions consistent with hypertensive retinopathy (e.g., retinal edema, intra-retinal serous exudation, retinal hemorrhages, arterial tortuosity, retinal detachment) are considered candidates for anti-hypertensive therapy. Angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril, benazepril) may have protective effects in patients with chronic renal disease due to their ability to block adverse effects of angiotensin II. Potential beneficial effects include reduction in proteinuria, limitation of glomerular sclerosis and slowing of progression of renal failure as well as improvement in systemic blood pressure. Enalapril (0.5 mg/kg PO q12h) typically is recommended in dogs with glomerular disease and hypertension, but enalapril has not been very effective for treatment of hypertensive cats. The calcium channel blocker, amlodipine has been used successfully to manage hypertension in cats at a dosage 0.625 to 1.25 mg per cat given orally once per day. Follow-up evaluations should be scheduled for one week after beginning treatment with amlodipine. Adverse effects (including hypotension) are very uncommon with the use of amlodipine in cats. In one study, amlodipine controlled hypertension in nearly 60% of CKD cats treated over a period of 3 months or more. Benazepril (0.5-1.0 mg/kg/day) may decrease proteinuria with minimal adverse effect on serum creatinine concentration in CKD cats. In one study of 192 cats, median survival in cats treated with benazepril (637 days) was not significantly longer than in those treated with placebo (520 days). However, when the small number of cats with urine protein/creatinine ratios $\geq$ 1.0 was considered, the difference in survival was more marked: 484 days for cats in the benazepril group (4 cats) versus 124 days for those in the placebo group (9 cats). Another study of CKD cats showed similar effects of benazepril on proteinuria with no difference in survival time between groups but some evidence of decreased rate of progression in the benazepril-treated group.

HORMONE REPLACEMENT: CALCITRIOL

Calcitriol may enhance gastrointestinal absorption of calcium and reduce parathyroid hormone (PTH) synthesis and secretion in cats with CKD. Calcitriol should not be administered until hyperphosphatemia has been controlled. If the Ca $\times$ P solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization. An extremely low dosage of calcitriol (2 to 3 ng/kg/day) has been used in cats with stable CKD to reverse renal secondary hyperparathyroidism. Plasma PTH concentrations decrease dramatically during calcitriol administration. Calcitriol is manufactured in capsule (250 or 500 ng) and liquid (1000 ng/ml) forms. Reformulation by a compounding pharmacy is necessary to provide accurate dosing. During treatment of CKD patients with calcitriol, simultaneous monitoring of serum ionized calcium and PTH concentrations is the ideal way to document successful and safe control of renal secondary hyperparathyroidism.

HORMONE REPLACEMENT: ERYTHROPOIETIN

Recombinant human erythropoietin (EPO) has been used to correct nonregenerative anemia in CKD cats. Treated animals demonstrate resolution of anemia, weight gain, improved appetite, improved haircoat, increased alertness, and increased activity. Therapy may be started in symptomatic cats with PCV values < 20%. The

starting dosage is 100 U/kg administered subcutaneously 3 times per week. Elemental iron supplementation should be provided at a dosage of 2 mg/kg/day, but some treated cats may experience gastrointestinal upsets. When the lower end of the target PCV range (30-40%) is reached, frequency of administration of EPO is reduced to twice a week. Depending upon the severity of anemia, it may require 3-4 weeks for the PCV to enter the target range. There is a high risk of anti-EPO antibody formation in cats receiving recombinant human EPO. Formation of antibodies against EPO may result in severe anemia and prolonged transfusion dependence. Although initially effective in correcting the anemia of CKD, use of recombinant human EPO is associated with antibody formation in up to 50% of treated animals after 1 to 3 months of treatment. The resulting anemia can be more severe than that present before treatment because the induced antibodies can cross-react with the animal's native EPO. Darbepoetin alfa has 5 added glycosylation sites and thus has a longer duration of action. It can be used at a lower dosage less frequently (0.5-1.0 mcg/kg subcutaneously once weekly) and may have a lower risk of antibody formation in cats. Potential adverse effects include vomiting, hypertension, and seizures. Feline recombinant EPO has been produced and shown to be effective, but unfortunately unexplained red cell aplasia developed in 26% of treated cats that had not previously been exposed to recombinant human EPO.

SUBCUTANEOUS FLUIDS AT HOME BY THE OWNER

Subcutaneous administration of crystalloid fluids (lactated Ringer's solution) to CKD cats by their owners at home assures optimal hydration and subjectively seems to improve the quality of life for many CKD cats. Some owners give a fixed volume each day (usually 120 ml) whereas others judge whether or not to administer fluids on a given day based on their observation of the cat's behavior (e.g. appetite, activity level, playfulness). The clinician should consider placement of a gastrostomy tube in CKD cats with poor appetites because this approach allows convenient delivery of calories, fluids, and medications and the tubes are well tolerated by most cats.

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