Treatment of Proteinuria: Maximally Reducing UPC

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Physiologic and hemodynamic determinants of urine protein excretion

The glomerular tufts are highly diversified capillary beds that permit filtration of large volumes of plasma and formation of urine. Non-glomerular capillary endothelium is relatively impervious to water and electrolytes; however, the glomerular endothelial cells have unique fenestrations which permit rapid trans-celleular fluid movement into Bowman's space. The unique composition and lattice-like pattern of collagen within glomerular basement membranes (GBM) also facilitates passage of some molecules into the ultrafiltrate, whereas others are specifically repelled by electric charge of GBM molecules. Finally, specialized cell junctions ('slight diaphragms') bridge the inter-podocyte cell filtration slits, resulting in a complex endothelium/GBM/podocyte filtration barrier that permits free movement of water and small dissolved solutes, retains a majority of serum proteins, and excludes cells and most other macromolecules.

Formation rate and composition of the ultrafiltrate (including protein excretion) is also influenced by intraglomerular hydrostatic forces. Glomerular filtration rate is individually maintained within each nephron by inversely regulating per-nephron renal plasma flow and transcapillary hydraulic pressure difference (i.e. the difference in pressure exerted by fluid in the capillary lumen versus the fluid within Bowman's space). When per-nephron regulation can no longer be maintained in animals with kidney injury, intraglomerular pressure increases will drive more fluid, dissolved molecules , and protein through the filtration barrier and into the ultrafiltrate. Proximal convoluted tubule cells will reabsorb most (but not all) excreted albumin in normal animals; when glomerular damage results in increased protein excretion, or PCT damage prevents reabsorption, urine protein dipsticks will register an increase in urine albumin.

Justification for reduction in proteinuria

Population-wide prospective studies have confirmed that excess urine protein is a biomarker for both the presence and severity of kidney injury. Additionally, these studies have occasionally suggested an association between both baseline ***and*** post-treatment urine protein concentration and patient prognosis, implying that rather than just monitoring proteinuria, active treatment is merited. People with chronic kidney disease (CKD) who excrete more than 3 g of albumin per day have a 8.1x greater risk of progressing to end stage renal disease (ESRD) than those who excrete less than 3g/day. Reducing proteinuria by >30% of baseline within 6 to 12 months of treatment predicts lower incidence of long term negative renal or cardiovascular outcomes in people with type 2 diabetes. Furthermore, with this disease the more protein excretion can be reduced, down to about 500 mg/day, the better the renal outcome.

Renal proteinuria has been associated with a greater risk of renal morbidity, renal mortality and all-cause mortality in dogs and cats as well. In dogs with chronic renal failure, pre-treatment urine protein: creatinine ratio (UPC) of >1.0 has been associated with a shorter length time until development of uremic crisis, and until death. In cats with chronic renal failure, a UPC ratio >0.4 at time of initial evaluation has been associated with increased risk of death due to any cause. In non-azotemic cats, proteinuria (UPC >0.3) is also associated with reduced survival (UPC ratio >0.3), and a reduction in renal proteinuria may be associated with more favorable patient outcome.

Pharmacologic Reduction of Proteinuria: RAAS Inhibition

Inhibition of the renin-angiotensin-aldosterone system (RAAS) reduces hydrostatic pressure within the glomerular capillary bed, and thereby decreases magnitude of proteinuria. Angiotensin converting enzyme-inhibitors (ACEi) are the mainstay drugs for RAAS inhibition in veterinary patients. However, angiotensin-II type I receptor blockers (ARB), aldosterone receptor antagonists (ARA), and renin inhibitors also decrease urine protein excretion.

Angiotensin-Converting Enzyme Inhibitors

Reduction of urine protein excretion by inhibition of angiotensin-converting enzyme (ACE) activity is the mainstay treatment for proteinuria of glomerular origin in dogs and cats. The best characterized benefit of these drugs is the reduction of protein excretion into the urine. Preferential vasodilation of the afferent renal areteriole is one of the compensatory mechanisms whereby individual nephron GFR increases during chronic renal failure. Reduction of systemic angiotensin II activation by inhibition of ACE results in further vasodilation, but in particular the preferential dilation of the efferent arterioles occurs over that of the afferent. This results in reduced intraglomerular hydrostatic pressure through a reduction in glomerular 'afterload.' The net effect is a reduction in the amount of filtrate (including protein) that passes into Bowman's space and eventually into the urine.

Although the reduction of intraglomerular hydrostatic pressure is the best characterized benefit of ACE inhibitors, additional benefits to this drug class have been identified. ACE inhibitors reduce mesangial cell hypertrophy in dogs with experimentally-induced glomerular disease either as an independent benefit of therapy or secondary to reducing intraglomerular hypertension. There is a general reduction in systemic arterial hypertension both via reduced angiotensin II concentration and reduced water and sodium retention (via reduced renin activation). Other mechanisms of vasodilation and modulation of inflammation includes prevention of bradykinin degradation, which promotes nitric oxide and prostacyclin production and further induces glomerular efferent arteriolar dilation. Which one(s) of these benefits is most critical for prolonging time until uremic crises or until death in dogs is unknown.

Enalapril is the most commonly used ACE-inhibitor (0.5 mg/kg q12-24h). A maximal reduction in proteinuria is desirable, so beginning with the maximum dose is recommended in non-azotemic patients. Adverse effects with this drug are uncommon. However because ACE-inhibitors reduce blood flow into the vasa recta, when treating severely azotemic animals (I worry when creatinine is >3.5) I begin with the longer dosing interval (q24h), recheck creatinine after four to seven days, and then increase to q12h if there has been no worsening in serum creatinine concentration. Other reported side-effects (which are definitely problematic in people) include hyperkalemia and anorexia due to gastrointestinal disturbances. In both cases withdrawal followed by restarting at lower doses can be attempted. In people, ACE inhibitor therapy is a relative-to-absolute contraindication for administration of NSAIDs because of the cumulative reduction in renal medullary blood flow; it is likely wise to avoid the combination of these drugs in veterinary patients as well.

Other ACE-inhibitors, including benazapril, lisinopril, captopril, ramipril, and quinapril are commercially available. There are very few studies directly comparing these drugs in the experimental setting, and none in animals with naturally-occurring disease. All of these drugs reach therapeutic serum concentrations with appropriate half-lives in healthy dogs with the exception of captopril. Benazapril is an attractive alternative to enalapril in veterinary patients because it in theory may be administered q24h with the same apparent effect as q12h enalapril, and because in experimental studies dogs with kidney disease did not require the same dosage adjustments that enalapril may require. However, there are several studies which provide indirect evidence that not all ACE-inhibitors can be relied upon to have equivalent effects in dogs with protein-losing nephropathies. For example, quinapril is more effective than enalapril in reducing severity of echocardiographic variables in Cavalier King Charles Spaniels with asymptomatic mitral regurgitation, serum enalaprilat (the active metabolite of enalapril) concentration

increases in dogs with sub-normal GFR, whereas benazeprilat does not, and captopril does not reduce serum ACE activity in healthy dogs as well as other ACE inhibitors. Therefore, I prefer enalapril over benazapril in dogs because the only study on the effects of ACE-inhibitors in dogs with naturally-occurring glomerular disease studied the benefits of enalapril…and why fool around with something that's definitely been shown to work?

Studies of cats with chronic kidney disease indicate that presence and severity of proteinuria may also associated with decreased long-term survival. Therefore treatment with ACE-inhibitors to reduce protein excretion may be beneficial (although results are conflicting). I choose to treat cats with chronic kidney disease and proteinuria with benazapril (0.5-1.0 mg/kg q24h), again, because the only efficacy study on ACE-inhibitors for reduction of proteinuria in cats was performed with this drug rather than enalapril.

Recommended enalapril dose (0.5 mg/kg q12h) is based on the pharmacodynamic end-point of plasma ACE activity reduction in healthy dogs to 25% of baseline. Although appropriate for initial dose establishment, human trials suggest that alternative pharmacodynamic goals requiring higher doses of enalapril (e.g. doses associated with maximal UPC, plasma angII, or aldosterone reductions) could dramatically improve patient survival times. Doubling of lisinopril dose in people with diabetic nephropathy further decreases UPC from 66% to 72% below baseline values, whereas patients with non-diabetic glomerular disease receiving standard vs. up-titrated dose of benazepril to minimize proteinuria had a 37.5% vs. 52.5% decrease in UPC below baseline; survival time was not determined in these studies, but as previously demonstrated, UPC in people is a reasonable surrogate. Effectiveness of the standard ACEi dose used in dogs is also questionable, as RAAS up-regulation in dogs with glomerular disease with hypoalbuminemia suggests that a higher dose that that derived from healthy dogs would be required. Unfortunately increasing enalparil dose is not risk-free: decreased intraglomerular hydrostatic pressure may reduce vasa recta blood flow, resulting in hypoxic kidney injury contributing to decreases in GFR. As such, any dose comparisons evaluating alternative pharmacodynamic endpoints should be done in patients with known baseline and resultant GFR.

Angiotensin II-Receptor Blockers

Although ACE-inhibitors are effective at reducing the severity of proteinuria in most dogs and cats with protein-losing nephropathies, it is not uncommon for the urine protein:creatinine ratio to still be above reference range in affected dogs even when the maximal drug dose is used. In order to further decrease proteinuria, some veterininary nephrologists have begun to use angiotensin II receptor blockers (ARBs, e.g. losartan) in those cases of severe proteinuria where ACE-inhibitors alone are insufficient. The reason why this double-pronged approach makes intuitive sense is because the little angiotensin II that is activated can be blocked by the use of ARBs. In addition, ARBs, and losartan in particular, may reduce the risk of thromboembolism in patients with severe proteinuria by interfering with angiotensin-II-mediate platelet activation.

However, whether or not concurrent use of ACE-inhibitors and ARBs truly offers any advantage beyond reduction of proteinuria is unclear. In people, ARBs and ACE-inhibitors are both used as first-line therapy for reduction of proteinuria; both classes of drugs have been documented to reduce UPC, reduce the rate of decline of renal function, and improve long-term outcome. However, concurrent use of a drug from each class, although further reducing UPC, does not seem to likewise further slow renal functional deterioration. In fact, the two drugs together have a higher risk of hyperkalemia (which may be severe), and in some studies the combination have actually lead to worsened outcome for patients with some glomerular diseases, particularly in the presence of concurrent cardiovascular disease.

Equivalent studies have not been performed in dogs as of yet, and as such ARBs are not advocated as first-line therapy, and it is unknown if combination treatment worsens, improves, or does not change prognosis. When used losartan (Cozaar®) is recommended at a starting dose of 0.5 mg/kg q12h. If creatinine has not increased more than approximately 30% after 4-7 days and the UPC is still increased,

then the dose is increased step-wise to 1-2 mg/kg q12h, again rechecking serum creatinine and UPC after each dose adjustment. Gastrointestinal side-effects have been anecdotally reported.

Aldosterone Receptor Antagonists

Serum aldosterone increases over time in people treated with maximal doses of ACEi and/or ARB time (termed 'aldosterone escape'), which may have adverse effects on the heart, systemic blood vessels and glomeruli. Aldosterone-receptor antagonists reduce proteinuria and stabilize kidney function in an additive fashion to ACEi and ARB in people. Spironolactone (1.0-2.0 mg/kg PO q 12 hrs) is used most commonly in veterinary medicine, however there is no published data examining its utility in the treatment of dogs or cats with glomerular disease. This drug likely would be most effective in animals with high serum aldosterone concentrations and persistent proteinuria in spite of treatment with an ACEi, ARB, or both. Anecdotal experience suggests that spironolactone is not very effective in reducing proteinuria in dogs with glomerular disease.

Dietary Therapy

Reduction in dietary protein has been shown to reduce urinary protein loss in *experimental* models of glomerular disease, primarily dogs with hereditary canine nephritis, and in the remnant kidney model in cats. Unfortunately whether this dietary therapy results in improved long-term prognosis and whether the reduction in proteinuria also occurs with *naturally-occurring* glomerular diseases is unknown. Preliminary results from one study did not show reduction in proteinuria in dogs receiving a protein-restricted diet, but the small number of dogs studied and lack of histologic subclassification has made interpretation of those results difficult. A more recent study compared survival in dogs with glomerular disease fed a renal-formulated diet in conjunction with benazepril to dogs fed benazepril alone. Again, this study has not been published in peer-reviewed format as of yet, but results suggested that there was in fact a long-term benefit to dietary therapy in animals with naturally-occurring glomerular disease,

Most nephrologists routinely recommend dietary therapy for patients with glomerular disease, regardless of whether or not they are azotemic. Severely protein-restricted diets likely do not provide increased advantage over the moderately-restricted diets. Commercial 'renal diets' are moderately protein restricted, and also have the advantage of sodium restriction and increased omega-3 fatty acid concentration which are theoretically advantageous in dogs with glomerular or tubular renal disease.