CANADA WEST
VETERINARY SPECIALISTS

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

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Physiology of the Renin-Angiotensin-Aldosterone System

The predominant role of the Renin-Angiotensin-Aldosterone System (RAAS) in the body is to control blood pressure. It achieves this by controlling fluid and electrolyte balance through actions on the heart, blood vessels, and kidneys. The main effector of the RAAS is angiotensin II. Angiotensin II also triggers release of aldosterone from the adrenal cortex. Angiotensin II is converted from angiotensin I by the action of ACE. Angiotensin I is converted from angiotensinogen by the action of renin. Renin is produced from the kidney when there is a decrease in renal perfusion.

Indications for the use of ACE Inhibitors and ARBs

There is strong evidence for the use of ACE inhibitors and ARBs in the treatment of proteinuria and for the use of ACE inhibitors in the treatment of congestive heart failure.

We also know that the RAAS is activated in chronic kidney disease and perpetuates renal injury. It does this by increasing glomerular pressure leading to proteinuria but more recently we have also realized that renin, angiotensin II, and aldosterone also induce a variety of pro-inflammatory and pro-fibrotic mediators. However, although the use of ACE inhibitors has been shown to improve proteinuria, we have as yet been unable to document a survival benefit for animals with non-proteinuric chronic kidney disease.

ACE inhibitors and ARBs have the potential to help with systemic hypertension although generally only to a modest degree and with a far less predictable response. For significant systemic hypertension, a combination of calcium channel blockers (e.g. amlodipine) and a RAAS inhibitor is therefore typically the preferred treatment. We are expecting some updated ACVIM guidelines on the management of hypertension to be published in the near future.

A study was recently presented at ECVIM looking at the use of telmisartan in testing for primary hyperaldosteronism in cats. Telmisartan was found to suppression aldosterone secretion in healthy cats but not in cats with primary hyperaldosteronism and therefore might hold promise as a diagnostic test. Further investigation will be needed.

Finally, given the finding that the RAAS system can be pro-inflammatory and pro-fibrotic, there is some interest in human medicine for the use of RAAS blockade for various inflammatory/ fibrotic conditions including arthritis and pancreatitis. We are probably a long way from treatment recommendations for such conditions in veterinary medicine.

We will focus on the use of ACE inhibitors and ARBs for the treatment of proteinuria for the remainder of these proceedings.

ACE Inhibitors

Angiotensin II acts on blood vessels to cause vasoconstriction, and works preferentially on the efferent arterioles of the glomerulus, resulting in increased glomerular pressure. ACE inhibitors therefore work to reduce proteinuria by improving systemic hypertension and glomerular hypertension. ACE inhibitors also prevent ACE-mediate degradation of bradykinin, which is a vasodilator. Additionally, there has been research in human medicine that ACE inhibitors can improve proteinuria by helping to maintain negatively charged proteins in the filtration membrane that are then able to repel negatively charged proteins in the blood. Finally, ACE inhibitors may potentially help with proteinuria given their suspected anti-inflammatory and anti-fibrotic effects.

The use of ACE inhibitors has been found to significantly decrease proteinuria and slow progression of proteinuric CKD. The most common ACE inhibitors used in veterinary medicine are enalapril and benazepril. Benazepril and its active metabolite, benazeprilat, are excreted primarily by the biliary route whilst enalapril and its active metabolite, enalaprilat, are eliminated primarily by the kidney. This would suggest that adjustments in enalapril doses might be required as kidney function progressively worsens although the pharmacokinetics of these ACE inhibitors seems too complicated to provide any definitive recommendations. The most recent ACVIM guidelines do not state a preference of enalapril or benazepril. There is a single study that suggested enalapril might be superior after 30 days of treatment although numbers in the study were small. I have historically preferred benazepril mainly due to the concern that progressive kidney dysfunction would have an unpredictable effect on enalapril plasma drug concentrations.

Although ACE inhibitors have been the main method of RAAS inactivation for decades, we have wondered about more effective options. The response of proteinuria to ACE inhibitors seems variable and we have discovered that angiotensin II, the main mediator of the RAAS, can be

produced by pathways other than ACE. Therefore ACE inhibitors do not provide complete RAAS blockade.

ARBs

There are two main angiotensin II receptors in the body: AT1 and AT2. AT1 is responsible for many of the vasoconstrictive and pro-fibrotic effects of angiotensin II, and for the release of aldosterone. The AT2 receptor actually mediates many opposite effects and is considered to have vasodilator and renoprotective effects. ARBs preferentially block AT1 whilst preserving the beneficial effects of AT2 and increasing the availability of angiotensin II for binding to AT2.

The most common ARBs used in veterinary medicine include losartan and telmisartan. Losartan was the first available ARB and has had some success in managing proteinuria in dogs but it has since been shown that dogs do not produce one of the more active metabolites of Losartan, EXP3174. Its pharmacokinetics (short half-life and small volume of distribution) also mean that Losartan is no longer recommended for use in dogs. Losartan is not thought to be effective in cats. Telmisartan appears to be much more beneficial and is the recommended ARB in dogs and cats.

Even ARBs do not provide complete RAAS blockade however; the use of ARBs has been shown to result in increased renin production over time.

Side effects

The major potential side effects of RAAS inhibitors include hyperkalemia, worsened azotemia, and systemic hypotension.

The use of a combination of ACE inhibitor and ARB allows for more complete RAAS blockade and has been shown to be beneficial in people. My experience with Losartan and an ACE inhibitor combined has anecdotally been disappointing. I do not currently have much experience with Telmisartan and an ACE inhibitor combined and further studies will be required. Combination therapy carries a much higher risk of the above side effects as would be expected and has been associated with a higher risk of death in people, particularly the elderly.

Practicalities of use

The use of an ACE inhibitor or ARB is generally indicated when the UPC is greater than 0.5 in dogs or greater than 0.4 cats, regardless of whether this represents a primary or secondary injury. Baseline lab work is recommended before considering the use of a RAAS inhibitor. Side effects of an ACE inhibitor and ARB seem most likely in animals with advanced or rapidly

progressive kidney disease and therefore careful consideration and monitoring is required in this population. An ACE inhibitor or ARB should be used with caution in the face of pre-existing hyperkalemia and likely avoided completely if the potassium concentration is greater than 6.5 mmol/L. The most recent consensus statement (ACVIM 2013) suggests that an ACE inhibitor should be the initial treatment for most dogs with proteinuria although given some impressive responses to telmisartan, and a generally variable response to ACE inhibitors, I am now selectively using telmisartan as a first line treatment for some patients. For ACE inhibitors, I generally start at 0.25mg/kg q12hrs and for telmisartan the generally recommended starting dose is 1mg/kg q24hrs.

I recommend a recheck serum chemistry 3-7 days after starting a RAAS inhibitor to monitor for hyperkalemia and worsened azotemia. Worsened azotemia is somewhat expected – it occurs due to decreased filtration pressure secondary to vasodilation of efferent arterioles in the glomerulus, which is also one of the methods in which these drugs reduce proteinuria. Increases in creatinine of greater than 30% from pre-treatment values should prompt discontinuation of the drug or a dose decrease and it is possible that animals with more advanced kidney disease may not be able to tolerate any worsening of azotemia at all. It would also be prudent to check blood pressure shortly after starting these drugs, although I have yet to document systemic hypotension.

The timing of evaluation of efficacy of treatment is variable in published recommendations. The most recent consensus guidelines (ACVIM 2013) suggest that bloodwork and UPC should be rechecked 1-2 weeks after starting to look for a response. However, there are some studies that suggest that RAAS inhibitors can take 30 days or more to demonstrate maximal response and therefore I generally recheck 1 month after starting or changing the dose.

The ideal goal of treatment would be for the UPC to return to within the reference range. However, this often ends up being unrealistic and therefore an alternate goal is to decrease the UPC by 50% of the starting value. It should be considered that there is significant day to day variation in UPC, particularly at higher values (>4). In one study, demonstration of a significant difference among serial values for UPC in proteinuric dogs required a change of at least 35% at high UPC values (near 12) and 80% at low UPC values (near 0.5).

If the goals of treatment are not met, it is reasonable to consider a dose increase. I generally increase ACE inhibitors by 0.5mg/kg/d up to a maximal dose of 2mg/kg/d or until side effects are recognized. I generally increase telmisartan by 0.25-0.5mg/kg/day and maximal doses are reported to be 5mg/kg/d although I have never used a dose this high. I recommend a repeat serum chemistry 3-7 days after a dose change to evaluate creatinine and potassium for evidence of side effects, and full re-evaluation to assess efficacy 1 month after the dose change.

If the treatment goal still isn't met, then switch to an alternative class of RAAS inhibitors

or combination therapy could be considered. The option of a kidney biopsy would also be reasonable at that time to evaluate if any other treatment options might be available.

Once stable, recheck is recommended every 3-6 months to monitor for progressive disease.