

Incorporating Angiotensin Receptor Blockers into Chronic Kidney Disease Management

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In patients with chronic kidney disease (CKD) altered kidney perfusion and filtrate formation activates the renin-angiotensin-aldosterone system (RAAS) resulting in the retention of sodium and water, systemic vasoconstriction and efferent glomerular arteriole vasoconstriction. Together these processes promote intraglomerular hypertension leading to glomerular injury and subsequent proteinuria. Renal tubular epithelial cells process these leaked proteins promoting the activation of inflammatory/vasoactive processes and mesangial proliferation causing tubulointerstitial nephritis, fibrosis, mineralization, and cell death. For this reason monitoring and managing hypertension and proteinuria induced by RAAS activation is essential to slowing renal injury.

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are two drug classes designed to reduce RAAS activation. While ACEi have been used routinely in veterinary medicine for decades, ARB use has slowly increased and a veterinary approved product is now available for managing feline hypertension in the United States. The purpose of this presentation is to discuss RAAS activation effects, the difference between the ACEi and ARBs mechanism of action, and the practical application of these drugs to kidney disease.

Renin-Angiotensin-Aldosterone System Activation

Through the actions of angiotensin II (AT-II) and aldosterone, RAAS maintains systemic homeostasis with regards to fluid balance, blood pressure, and electrolyte concentrations. Systemic AT-II production begins with the release of renin from kidney juxtaglomerular cells in response to reduced renal blood flow and tubular filtrate flow. Renin catalyzes angiotensinogen to angiotensin I (AT-I) which in turn is hydrolyzed by circulating and endothelial associated angiotensin converting enzyme (ACE) to form AT-II. Alternate pathways of AT-II generation also exists within certain tissues such as the heart and kidney using enzymes such as chymase. These ACE independent pathways provide a mechanism for producing AT-II even when ACE is inhibited. This is called ACE-escape.

Once formed AT-II binds to type 1 (AT₁) and type 2 (AT₂) receptors. Stimulation of the type 1 receptor (AT₁) is primarily responsible for systemic vasoconstriction, constriction of the glomerular efferent arteriole, and aldosterone production by the adrenal glands. These AT₁ effects increase systemic blood pressure, increase intraglomerular pressure and filtrate formation, and increase salt and water retention to increase blood volume. Stimulation via the AT₂ receptor has many renoprotective effects including promoting vasodilation, natriuresis, anti-inflammatory and antifibrotic effects.

Renin-Angiotensin-Aldosterone System Inhibition

In CKD chronic RAAS activation has numerous detrimental effects including systemic hypertension, increased intraglomerular pressure, glomerular enlargement, and proteinuria. Although it is possible to block RAAS at many points along its pathway in veterinary medicine ACEi are commonly reached for to manage hypertension and proteinuria. ACEi such as enalapril and benazepril inhibit the ACE mediated conversion of AT-I to AT-II and ACE degradation of bradykinin. Systemically the primary effect of ACEi is vasodilation. Locally at the level of the kidney ACEi promote efferent arteriole dilation thereby reducing intraglomerular pressure, glomerular hyperfiltration, and proteinuria. Long-term use of ACEi in dogs with CKD is beneficial as it has been shown to slow the progression of glomerulosclerosis and tubulointerstitial lesions.

In contrast ARBs (telmisartan and losartan) block the action of AT-II specifically at the AT₁ receptor. This alternate mechanism of RAAS inhibition has two benefits. First, by inhibiting only AT₁ signaling the renoprotective AT₂ receptor signaling is preserved. Second, since ARBs act at the level of receptor binding, they are able to block the action of AT-II regardless of whether it is produced systemically by ACE or locally by alternate enzymes. This may help prevent the ACE-escape seen with the use of ACEi however additional clinical studies in dogs and cats are required to prove superiority to ACEi. Regardless, the clinical benefits of telmisartan appears to

be similar to ACEi and in cats the telmisartan has been proven to be effective at reducing blood pressure and proteinuria.

Practical Application of ACEi and ARBs

Given their vasodilatory properties both systemically and at the level of the glomerular afferent arteriole, ACEi and ARBs are valuable tools in managing patients with hypertension and/or glomerular proteinuria. The expected antihypertensive effects can vary depending on the species and class of drug used, however a reduction in blood pressure of 10-15% is generally expected. In proteinuric patients (UPC >0.2 in dogs and >0.4 in cats) ARBs and particularly ACEi are standard of care. Depending on the underlying pathology causing the glomerular proteinuria or hypertension, the effect of RAAS inhibition can vary and hence treatment recommendations for cats and dogs also vary.

In dogs hypertension is commonly associated with CKD and proteinuria. Given the importance in controlling both of these pathologies in patients with CKD, the dual benefit RAAS inhibitors provide make ACEi and ARBs a good first choice. Historically ACEi have primarily been used given that studies have demonstrated that enalapril/benazepril successfully reduce proteinuria, reduce progression of tubulointerstitial lesions, and improve CKD outcome. Starting doses of 0.25-0.5mg/kg PO q12h of enalapril and benazepril are common with a titration to up to 2.0mg/kg/d possible to control hypertension. ARBs like telmisartan are now being used as a therapeutic alternative starting at a dose of 1mg/kg PO q24h. However, to date there has been limited studies in dogs demonstrating ARB superiority to ACEi for the treatment of hypertension and proteinuria.

In general, ACEi and ARBs are weak antihypertensive drugs. In dogs with evidence of end organ damage or systemic blood pressures >200mmHg monotherapy with an ACEi or ARB is unlikely to reduce blood pressure sufficiently. In these instances co-administration with amlodipine is recommended. Amlodipine is a calcium channel blocker that acts on vascular smooth muscle, particularly the arterioles, resulting in vasodilation, primarily of the afferent arteriole. Theoretically this effect could be dangerous because if pressures are not adequately controlled the dilated afferent vessel may become a conduit in which high systemic pressures can be directly imposed on the glomerulus furthering renal damage. Combination therapy of amlodipine with an ACEi or ARB is considered ideal since amlodipine dilates the glomerular afferent arteriole and ACEi/ARBs preferentially dilate the efferent arteriole thereby limiting the potential detrimental effect of one or the other on glomerular hydrostatic pressures.

In cats amlodipine remains the recommended first-line therapy for hypertension regardless of cause given its proven efficacy. Unlike in dogs, amlodipine is often given as a sole agent. The justification is related to limiting pill burden rather than being pathophysiological as amlodipine has not been proven to improve survival times and activates RAAS. For that reason, in cats, particularly those with proteinuria, combination therapy with ACEi or ARBs may be beneficial. Benazepril in particular has been demonstrated to reduce proteinuria and glomerular capillary pressures in cats with CKD.

Unfortunately, in naturally occurring hypertension ACEi have not been proven to be particularly effective agents in reducing hypertension in cats. Studies have revealed only marginal improvements in systolic blood pressure (~10mmHg) and hence ACEi use as antihypertensive agents is generally not recommended unless the goal of therapy is to reduce proteinuria. In contrast the ARB telmisartan at a dose of 2mg/kg/d significantly reduced systolic blood pressures in hypertensive cats with nearly ½ of patients reducing their blood pressure by >20mmHg. This study did exclude cats with blood pressures >200mmHg and hence combination therapy with amlodipine is recommended if a RAAS inhibitor is used to treat marked hypertension. Although the evidence is limited, combination therapy with amlodipine and telmisartan does appear safe and effective.

Alternatively, in some patients, particularly dogs with proteinuria, the combined use of an ACEi and ARB can be considered when ACEi dosages are maximized. Their combined use has not been extensively studied in cats and dogs and must be used cautiously as the risk of side effects may increase and in one human study combined ACEi and ARB use was associated with increased risk of death. The main concerns associated with ACEi and ARB use is that the resultant dilation of the glomerular efferent arteriole may decrease glomerular pressures. This

effect can lead to a decrease in GFR and may be accompanied by a mild increase in the magnitude of the azotemia in dogs and cats. For this reason initiating ACEi or ARB therapy in a patient that is dehydrated, hemodynamically unstable, or in patients with unstable renal disease is not recommended. That said, there has been proven a clinical benefit of using ACEi in dogs with CKD and hence the presence of stable azotemia should not dissuade one from using these drugs. In general, in cats and dogs with CKD ACEi or ARBs therapy can be utilized in stage 1 and 2 CKD patients with hypertension and/or proteinuria. In stage 3 and 4 CKD their use should be approached more cautiously utilizing a lower starting dose (typically $\frac{1}{2}$ the normal starting dose). If upon starting an ACEi or ARB the azotemia worsens by 30% or more then the dosage is reduced or drug discontinued. Other side effects to consider are that the RAAS inhibition can induce hyperkalemia while the resultant vasodilation can result in hypotension, weakness, and lethargy.