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DIFFERENTIATION OF CARDIAC AND RESPIRATORY DISEASE IN THE DOG

ADVANCES IN THE MANAGEMENT OF CANINE HEART FAILURE

ACE-INHIBITORS AND AZOTEMIA IN DOGS WITH HEART DISEASE
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In landmark veterinary studies of enalapril in NYHA phase III and IV heart disease (moderate to severe heart failure), due to mitral regurgitation (MR) and dilated cardiomyopathy (DCM), enalapril improved survival by >100% as well as reducing pulmonary edema and, improving quality of life scores.\textsuperscript{1-3} Exercise capacity is also improved in dogs with experimental mitral insufficiency.\textsuperscript{4} Benazepril has likewise been shown to improve survival.\textsuperscript{5} ACE-I have proven to provide additional benefits in human patients by blocking pathological remodeling, presumably slowing progression of heart disease and by normalizing serum electrolyte concentrations. Today, ACE-I represent the cornerstone in the chronic management of CHF. They are indicated in virtually all cases of systolic heart failure in which they are tolerated.

There was early concern regarding the renal safety of these compounds \textsuperscript{6-8} and all ACE-I, which have enjoyed extensive clinical use, have been associated with renal dysfunction, usually temporary.\textsuperscript{9} There has been speculation that, at very high doses (180x the clinical dosage), ACE-I have direct nephrotoxic effects but it is generally felt that the major impact of ACE-I on the kidney, with clinically relevant dosages, is through production of hypotension, with reduced renal perfusion pressure and resulting in worsening of azotemia.\textsuperscript{10} To date, veterinary clinicians have had experience with enalapril, captopril, benazepril, imidipril, ramipril and lisinopril. Of these, only enalapril has been extensively studied and is licensed for use in management of heart failure in the United States, though benazepril has been marketed in Europe and Canada. The active metabolite of benazepril is reportedly excreted both in the bile and in the urine so that lower serum concentrations are evident in experimental renal disease.\textsuperscript{11} The clinical relevance of this is unclear. Over 10 years of veterinary clinical experience with ACE-I (mainly captopril and enalapril) have taught us that their impact on kidney function is minimal even in the face of severe heart failure. When azotemia is observed, ACE-I are almost always being used in conjunction with diuretics and sodium restriction and hypotension results. Typically, cessation of diuretic therapy or reduction in the dosage results in the reversal of azotemia.\textsuperscript{9}

In studies of enalapril in NYHA phase III and IV heart disease (moderate to severe heart failure), due to MR and DCM, there was actually a lower incidence of azotemia in the enalapril-treated group than the placebo-treated group.\textsuperscript{1-3,12} Furthermore, in a study of enalapril's role in the delay or prevention of heart failure due to naturally-occurring MR, showed that enalapril at the standard dosage of 0.5 mg/kg daily had no effect on serum creatinine concentrations, as compared to placebo.\textsuperscript{13}
In fact, evidence is building to prove benefit when ACE-I are administered chronically to both human and veterinary patients with naturally-occurring and experimental renal failure.\textsuperscript{14-20} Mechanisms for this improvement are postulated to be the antihypertensive effect, reduction of angiotensin II-induced mesangial cell proliferation, and renal vasodilatory effects of ACE-I, the latter related to a fall in renal filtration pressure and proteinuria.\textsuperscript{14-16} Enalapril has recently been shown to reduce urine protein loss and reduce blood pressure in naturally-occurring canine glomerulonephritis.\textsuperscript{18} Likewise, benazepril reduced azotemia and proteinuria in a short-term study of experimental and naturally-occurring renal insufficiency in cats\textsuperscript{19} and lowered BUN and creatinine concentrations and blood pressure in cats with polycystic kidney disease.\textsuperscript{20}

As mentioned above, ACE-I have the potential to produce symptomatic hypotension. This is due to the mixed vasodilatory effect of this group of drugs and is typically observed when ACE-I are used in conjunction with other off-loading therapies, such as vasodilators, diuretics, and sodium restriction. Hypotension is reversed by altering drug therapies but may be problematic in producing azotemia, inappetance, weakness, lassitude, and precipitating digitalis intoxication by reducing renal elimination.

REFERENCES


