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Angiotensin-Converting Enzyme Inhibitors and Cardiac Disease: Have They Had Their Day?

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Some 30 years ago, the veterinary cardiology profession embarked on a series of clinical trials to examine the efficacy of angiotensin-converting enzyme inhibitors (ACE-I) in the management of canine heart disease. A generation of veterinarians have used ACE-I in their daily practice. Many have believed that these drugs have prolonged the survival of dogs and cats with heart disease. They were taught to give it to dogs (and cats) with congestive heart failure (CHF), then to give it to all dogs with murmurs, then to give it to dogs with subclinical cardiomyopathy. Drug companies sold millions of dollars worth of these drugs to pet owners. Was it all in vain? Were veterinarians sold "a bill of goods"?

The results of studies in humans prompted the veterinary community to embark on a series of studies to examine whether these drugs (specifically, enalapril) could confer similar benefits to dogs (and, to a much lesser degree, cats). Based on the results of these studies, enalapril was licensed for treating dogs with CHF and promoted for use in dogs prior to the onset of CHF. But what did these studies really show? Were veterinarians hoodwinked into believing the data because we needed new therapies? Thirty years later, with the aid of retrospectroscopy, we can assess just what transpired.

"If ACE-I have any role in managing heart disease, it is restricted to dogs with DCM."

CANINE CLINICAL TRIALS

The first randomized clinical trials of ACE-I in dogs were, to be fair, groundbreaking in as much as they were likely the first large clinical trials in pets. All of these were funded by the manufacturer of enalapril, Merial. The first of these studies, IMPROVE (Invasive Multicenter PROspective Veterinary Evaluation of enalapril), randomized 58 dogs with CHF, of which 41 completed the study: 18 with myxomatous mitral valve disease (MMVD), 23 with DCM) to receive either enalapril, or placebo, over a 3-week period.[1] Somewhat perplexingly, the tables in the published article show responses for 51, rather than 41, dogs, making interpretation of data problematic. However, even if we take the tabulated data at face value, it becomes immediately clear that the majority of benefit, if one existed, occurred in the DCM group, not the MMVD group.

The IMPROVE study was coupled with the COVE study (COntrolled clinical eValuation of Enalapril).[2] This study enrolled a much larger cohort of dogs with CHF caused by either MMVD or DCM, randomized to receive either enalapril or placebo. Again, examination of Tables 7 and 8 in that article showed that almost all statistically relevant improvement occurred in dogs with DCM, not MMVD. Some might argue that these studies were not powered to detect effects in the disease subgroups. However, the investigators performed this analysis, and in the COVE study, dogs with DCM represented 30% of the total cohort. Therefore, the dogs with MMVD had a much greater chance of demonstrating an effect of the drug similar to that seen in the DCM group.

The LIVE (Long-term Investigation of Veterinary Enalapril) study completed the initial enalapril "trilogy" studies funded by Merial.[3] This study examined the long-term survival of dogs with either MMVD or DCM, again randomized to receive either enalapril or placebo. The published results suggested that dogs with MMVD, but not DCM, survived longer or had stable CHF longer if receiving enalapril. However, subsequent investigations of the data showed that when the study was presented some 4 years prior to publication, the exact opposite had been observed—in other words, the dogs with DCM receiving enalapril did better than those on placebo. The drug had no effect on outcomes in dogs with MMVD. What happened between the presentation and the publication? All that we know is that 21 of the dogs with MMVD and 17 of the dogs with

DCM in the initial cohort, presented prior to publication, had "disappeared" from the final analysis. When the lead investigator of this study was asked why this had occurred, he replied that the drug company had taken the data and analyzed it without informing the investigators, who merely participated as case recruiters and clinicians.

Why would a drug company want to "lump" MMVD dogs together with DCM dogs? Why would they show results for "all dogs in CHF," when the data clearly showed the effect was limited to the DCM cohort in three separate studies? The answer is obvious—it's all about the money! There are 100 to 1,000 times more dogs in the world with MMVD than DCM. Therefore, selling the drug for management of congestive failure in MMVD will generate massively greater revenues than selling the drug to owners of dogs with DCM. In retrospect, it became clear that the veterinary community was hoodwinked into believing that ACE-I were the medical cure for CHF dogs because of corporate marketing decisions.

Soon after these three studies were published, interest arose in seeing if enalapril could help dogs with subclinical MMVD. After all, for every dog with MMVD that had CHF, there were 3 to 5 dogs with subclinical MMVD! If companies could reach that market, the profits would skyrocket. And so, studies examining the ability to delay the onset of CHF began.

The first of these, the SVEP (Scandinavian Veterinary Enalapril Prevention) trial, randomized Cavalier King Charles Spaniels with subclinical MMVD to receive either enalapril or placebo.[4] Dogs were followed until they developed CHF or died from a cardiac cause. The study showed that enalapril had absolutely no effect on preventing development of CHF in this group of dogs.

However, concerns arose that (i) the dose was too low to observe an effect (even though the dose prescribed was the dose licensed by the drug manufacturer) and (ii) Cavalier King Charles Spaniels are not representative of other small-breed dogs with MMVD. Consequently, the VETPROOF (Veterinary Enalapril Trial to Prove Reduction in Onset of heart Failure) study was undertaken.[5] This study enrolled dogs of various breeds, randomized to enalapril or placebo. Again, despite the authors' best efforts, the drug failed to demonstrate a benefit in delaying the onset of CHF or cardiac death.

Because enalapril might be helping dogs with DCM that have CHF, a "prevention" study was published in 2009.[6] This study was retrospective and came with all the concerns and inherent biases that retrospective studies carry. The investigators examined Doberman Pinschers with subclinical DCM and found that the ACE-I prolonged time to onset of CHF by approximately 100 days. While the dogs in the ACE-I group appeared to be as badly (or more severely) affected than those in the no-treatment group at enrollment (which is a positive for retrospective

studies), almost one-third of the dogs in the ACE-I group were also receiving beta blockers, compared to 3% of the dogs in the control group. Given that beta blockers have been proposed in humans with myocardial failure to exert benefits on outcomes, the findings could be, at least in part, affected by the concomitant use of beta blockers in the ACE-I group. The authors rightly suggested that prospective studies might be warranted to verify their findings; however, none have been undertaken.

ACE-I IN CATS

What about ACE-I in cats? Virtually no data existed about the benefits (or lack thereof) of ACE-I in cats with heart disease until 2019. Recently, a study of the use of benazepril in cats appeared, showing that the drug failed to benefit cats with various forms of heart disease, with or without CHF.[7] The study enrolled 151 cats, randomized to receiving benazepril or placebo. Although the study was poorly designed in terms of case selection and recruitment, the authors could not find any benefit in either delaying onset of CHF or preventing worsening of CHF. However, the most interesting feature of this study was the years during which the study was recruiting and monitoring cats—2003 to 2005. It became clear that the study was not presented, discussed, or published for another 14 years after it ended, because it would negatively impact the sales of benazepril to veterinarians treating cats with heart disease.

CONCLUSIONS

So, what does all this mean? My interpretation of all this literature suggests that ACE-I have no place in managing mitral valve disease, whether in dogs with CHF or dogs with subclinical disease. Similarly, they have no place in managing cats with heart disease. If ACE-I have any role in managing heart disease, it is restricted to dogs with DCM (either subclinical or with CHF). However, whether the benefit of ACE-I in dogs with DCM persists in the era of pimobendan remains unknown. It is possible that pimobendan provides all the benefit that one will likely see and that ACE-I have no additional effect. It might be time to move ACE-I into the same pile as theophylline and digoxin when it comes to managing progression of disease or stabilizing CHF.

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