PIMOBENDAN A NEW DRUG FOR HEART FAILURE MANAGEMENT

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Dilated cardiomyopathy (DCM) represents the second-most common acquired cardiac disease of dogs with acquired degenerative the other disease being the most common cause of heart failure by far. Dilated cardiomyopathy is a primary myocardial abnormality which in most cases has no demonstrable etiology. Although a relatively small number of dogs have been documented to have myocardial taurine or carnitine deficiencies this population makes up a very small percentage of the total number of dogs afflicted with this disease. This disease may go undetected in the earlier portions of its progression. Early forms of dilated cardiomyopathy manifest as having only mild cardiac dilation without overt evidence of myocardial systolic dysfunction. Although not invasive indices of systolic function may be normal at this time, this may simply represent a relatively crude methods by which we evaluate systolic function in a non-invasive manner. Detection of early evidence of systolic dysfunction has recently been re-emphasized due to the possibility that intervention in this so-called occult stage of the disease may have substantial survival benefit. Unfortunately the vast majority of patients are not diagnosed until clinical signs are evident.

Clinical signs are most notably associated with either accumulation of fluid in the lung or abdominal space manifest as ascites or pulmonary edema. Some astute clients notice evidence of exercise intolerance or increased resting respiratory rate prior to onset of overt congestive heart failure. Since affecting a cure for these patients is unrealistic our goals are to improve quality of life by eliminating clinical signs and ideally to increase longevity. When managing heart failure, there are a small number of general interventions that can be utilized in an attempt to optimize cardiac output while eliminating signs of fluid accumulation. There are actually four major categories of therapy that can be employed when managing heart failure. Our goal is to maintain adequate cardiac output to provide needed blood flow while reducing the likelihood that clinical signs of congestion are present. General approaches to the manipulation of the relationship between filling pressure (the driving force for edema accumulation) and forward cardiac output are to 1) optimize filling, 2) decrease afterload, 3) optimize heart rate and rhythm and 4) improve contractility.

The majority of recent interventions have concentrated efforts at unloading the ventricle essentially making it easier or for the heart to pump forward and/or by optimizing filling most notably through reductions in heart rate and relaxation of the myocardium. Indirectly, medications such a spironolactone and perhaps ACE inhibitors may reduce fibrosis long-term, thereby improving cardiac filling. Long-term therapy with positive inotropic agents has gotten less attention. This may in part be due to the fact that the only oral positive inotrope routinely utilized in veterinary medicine is digoxin. Digoxin is known to have a very narrow therapeutic window and to be in exceptionally weak positive inotropic action. Additionally one of the concerns with long-term oral positive inotropic therapy has been that because of the mechanism of these agents (calcium loading via multiple variable mechanisms) predisposition to arrhythmias may preclude the long-term management with these agents and ultimately lead to decreased short-term survival.

Pimobendan is a unique therapeutic cardiotonic tonic agent possessing both inotropic and vasodilatory properties. Pimobendan has a selective phosphodiesterase III inhibitory action providing its vasodilatory properties. Additionally, pimobendan sensitizes myocardial contractile proteins to calcium with resultant positive inotropic properties. Since pimobendan does not lead to myocyte loading with calcium, the likelihood of arrhythmias (the limiting effect of many positive inotropes) can be minimized. In human clinical trials pimobendan has been well tolerated and associated with improved exercise tolerance during the first six months of therapy with an insignificant trend towards increased mortality.

There have been several important clinical trials evaluating the efficacy of pimobendan, both in dogs with the valvular heart disease and in dogs with dilated cardiomyopathy. One of note was a double-blind randomized placebo-controlled study of pimobendan in dogs with dilated cardiomyopathy reported by Fuentes et al. In this study 10 Doberman pinschers and 10 English cocker spaniels with dilated cardiomyopathy were evaluated with pimobendan or placebo administered in addition to standard background therapy of furosemide, enalapril with or without digoxin. While pimobendan had no significant effect on survival in the cocker spaniels, the Doberman pinschers treated with pimobendan had significant longer survival time compared to those receiving placebo. The median survival time of 329 days was seen in the pimobendan group compared with 50 days in the placebo group. Based on the results that study the authors concluded that pimobendan significant improves heart failure class when added to standard therapy in dogs with dilated and appears to contribute to improve survival in Doberman pinschers.