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Effect of pimobendan on the incidence of arrhythmias in small breed dogs with myxomatous mitral valve degeneration

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Abstract *Objective:* To determine if pimobendan, a phosphodiesterase III inhibitor and calcium sensitizer with positive survival benefits, has an effect on incidence of arrhythmias compared to placebo in small breed dogs with congestive heart failure (CHF) due to myxomatous mitral valve degeneration (MMVD).
Animals: Eight client-owned small breed dogs (<15 kg) with CHF due to MMVD.
Methods: A prospective double-blind randomized placebo-controlled crossover study design was used. Data were recorded at baseline and 2 weeks post-administration of placebo or pimobendan. Average heart rate and incidence of arrhythmia were determined from 24 h Holter analysis. Owners completed a quality of life (QOL) questionnaire at each time point and recorded sleeping respiratory rates (SRR). Mixed effects analysis of variance, with dog as the random variable was used to compare values obtained between baseline, placebo, and pimobendan.
Results: Compared to baseline, QOL scores were significantly improved following administration of either placebo or pimobendan ($p = 0.021$ and $p < 0.001$, respectively). No significant differences in type or incidence of supraventricular or ventricular arrhythmia were identified. Average heart rate with pimobendan was significantly lower than baseline ($p < 0.001$). Compared to baseline, SRR was significantly lower with pimobendan ($p = 0.004$), and significantly different from placebo ($p = 0.045$).

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Conclusions: No significant difference between pimobendan and placebo was found on incidence of supraventricular or ventricular arrhythmia. The decrease in average heart rate and SRR may be reflective of superior heart failure control achieved with pimobendan therapy.
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Abbreviations

ACEi	angiotensin converting enzyme inhibitor
APC	atrial premature complex
CHF	congestive heart failure
ECG	electrocardiogram
MMVD	myxomatous mitral valve degeneration
QOL	quality of life
SRR	sleeping respiratory rate
VPC	ventricular premature complex

Introduction

Pimobendan is a benzimidazole-pyridazinone derivative that functions as an arteriodilator, venodilator, and positive inotrope, and is therefore classified as an inodilator. It exerts its effects via inhibition of phosphodiesterase III and calcium sensitization.[1] Pimobendan has been shown to have positive benefits in humans, and dogs with congestive heart failure (CHF) due to myxomatous mitral valve degeneration (MMVD).[2–6,c] Initial clinical trials of pimobendan in humans demonstrated a trend towards increased incidence of arrhythmia-related sudden death, which led the FDA to deny the drug a license for human use.[3] However, more recent human clinical trials demonstrated that pimobendan resulted in a significant improvement in quality of life (QOL) and decreased morbidity, with no increase in risk for sudden death for symptomatic non-ischemic cardiomyopathy patients with no prior history of arrhythmia.[7] Assessing the effect of pimobendan on arrhythmia type and frequency in dogs with CHF secondary to MMVD is therefore warranted and has the potential to impact clinical decisions related to timing of drug initiation relative to disease time course.

The literature concerning incidence of arrhythmia and sudden death in dogs with CHF treated with pimobendan is conflicting. One study found no difference in percent change in the frequency of ventricular premature complexes (VPCs) per hour between dogs with CHF due to MMVD receiving either pimobendan or benazepril although the frequency of arrhythmias between dogs was highly variable and the study was limited by the lack of cross-over design.[2] Similarly, the QUEST study demonstrated a prolonged time to reach the composite primary endpoint of cardiac death, euthanasia as a consequence of cardiac disease, or treatment failure with pimobendan, and also documented no difference in incidence of arrhythmia compared to benazepril.[5] However, analysis of arrhythmias in the study was limited to a 3 min in-hospital electrocardiogram (ECG), and the number of dogs experiencing sudden death in each group was small. In a study evaluating dogs treated with pimobendan or ACE inhibitor (ACEi), both groups had increased VPCs and atrial premature complexes (APCs) over the duration of the study based on 5-min ECG in a small number of dogs.[4] Similarly, a second study found a higher frequency of VPCs in dogs receiving pimobendan, however, the effect of worsening disease severity during the course of the trial was not accounted for in the study design.[c] Consequently, limitations exist with previous veterinary studies designed to assess the effects of pimobendan on incidence of arrhythmia.

The purpose of this study was to assess the effect of pimobendan administration on type and frequency of arrhythmias in dogs with CHF due to MMVD. In addition, QOL was assessed throughout the study using a previously validated QOL questionnaire.[8] Finally, sleeping respiratory rate (SRR) and average heart rate were monitored as indirect indicators of heart failure control. With the increasing use of pimobendan in dogs with CHF, the effect of this drug on incidence and type of arrhythmia becomes increasingly important due to the large numbers of dogs with CHF due to MMVD exposed to this medication.

Animals, materials and methods

Study population

Eight client-owned, small-breed (<15 kg) dogs in stable medically controlled CHF due to MMVD were

[c] Rosenthal SL, Lefbom BK, Tyrrell WD. Association of pimobendan with ventricular arrhythmias in dogs with congestive heart failure. J Vet Intern Med 2006; 20:731 (abstract).