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Effect of Pimobendan on Case Fatality Rate in Doberman Pinschers with Congestive Heart Failure Caused by Dilated Cardiomyopathy

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Background: Despite traditional therapy of a diuretic, angiotensin converting enzyme inhibitor, digoxin, or a combination of these drugs, survival of dogs with dilated cardiomyopathy (DCM) is low. Pimobendan, an inodilator, has both inotropic and balanced peripheral vasodilatory properties.

Hypothesis: Pimobendan when added to conventional therapy will improve morbidity and reduce case fatality rate in Doberman Pinschers with congestive heart failure (CHF) caused by DCM.

Animals: Sixteen Doberman Pinschers in CHF caused by DCM.

Methods: A prospective randomized, double-blind, placebo-controlled study with treatment failure as the primary and quality of life (QoL) indices as secondary outcome variables. Therapy consisted of furosemide (per os [PO] as required) and benazepril hydrochloride (0.5 mg/kg PO q12h) and dogs were randomized in pairs and by sex to receive pimobendan (0.25 mg/kg PO q12h) or placebo (1 tablet PO q12h).

Results: Pimobendan-treated dogs had a significant improvement in time to treatment failure (pimobendan median, 130.5 days; placebo median, 14 days; $P = .002$; risk ratio = 0.35, $P = .003$, lower 5% confidence limit = 0.13, upper 95% confidence limit = 0.71). Number and rate of dogs reaching treatment failure in the placebo group precluded the analysis of QoL.

Conclusions and Clinical Importance: Pimobendan should be used as a first-line therapeutic in Doberman Pinschers for the treatment of CHF caused by DCM.

Key words: Congestive heart failure; Dilated cardiomyopathy; Doberman Pinscher; Mortality; Pimobendan.

Dilated cardiomyopathy (DCM) is the second most common acquired heart disease in dogs and represents a significant cause of morbidity and mortality in certain breeds, including the Doberman Pinscher, Scottish Deerhound, Irish Wolfhound, Great Dane, Saint Bernard, Afghan Hound, Newfoundland, Old English Sheepdog, and English and American Cocker Spaniels.[1–3] In North America, the Doberman Pinscher is the most commonly affected breed, with the frequency of developing DCM estimated at 41% for males and 31% for females.[4]

DCM appears to progress through 3 distinct phases in affected Doberman Pinschers: the 1st phase is characterized by a morphologically and electrically normal heart in a symptom-free dog; the 2nd phase is characterized by evidence of morphological (cardiac enlargement) or electrical (ventricular ectopy) derangement in a dog that is otherwise free of clinical signs (occult disease); and finally, the 3rd phase is overt congestive heart failure (CHF), characterized by clinical signs of forward or backward flow failure.[4,5] Whereas dogs with occult disease can have a protracted disease time course (up to 4 years), overt DCM in the Doberman Pinscher is rapidly progressive, with mean and median survival estimates of 11 and 7.5 weeks, respectively, despite therapeutic intervention.[6] Additionally, Doberman Pinschers that develop atrial fibrillation or ascites as complications to left-sided or biventricular failure have a poorer prognosis, with a median survival of 3 weeks and 8.5 days in 2 studies.[6,a]

Pharmacologic intervention remains the most effective treatment modality for dogs and focuses on modulating preload, afterload, and systolic function (contractility). However, despite the relatively common occurrence of DCM, debate remains as to the most effective long-term pharmaceutical protocol, in terms of both therapeutic agent(s) and time of therapeutic intervention. To date, there is only 1 peer-reviewed study demonstrating a statistically significant improvement in quality of life (QoL) for dogs with DCM. This involved treatment with an angiotensin converting enzyme inhibitor (ACEI; enalapril) over a 28-day treatment period.[7] There have been no published studies confirming that any of the current commonly used pharmacologic interventions, including furosemide, ACEIs, or digoxin, improve survival in dogs with DCM, despite a significant amount of supportive data from the human literature.[8–10] Complicating this clinical picture is work that suggests a role for the use of ACEI in occult disease.[b] As a result, various other pharmaceuticals are being investigated in an effort to improve upon QoL as well as long-term prognosis of dogs with heart failure caused by DCM.

Pimobendan is a phosphodiesterase (PDE) III and V inhibitor with calcium sensitizing properties that mediates both inotropic and balanced peripheral vasodilating actions.[11] In the healthy heart, the PDE III inhibitory action of pimobendan is largely responsible for the positive inotropic effect; however, during heart failure and down-regulation of adrenergic receptors, the calcium sensitizing effects predominate, resulting in positive inotropy via enhancing the affinity of myocardial troponin C

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to existing intracellular calcium.[12–15] Unlike historical PDE III-positive inotropes, including milrinone and amrinone, pimobendan improves contractility without the attendant increased myocardial oxygen or energy requirements.[16] Peripherally, pimobendan's PDE III inhibition results in balanced peripheral vasodilation through increased efflux of intracellular calcium from vascular smooth muscle; as a PDE V inhibitor, it has pulmonary arterial vasodilating properties.[11,17] With balanced vasodilation reducing cardiac work via reductions in preload and afterload, coupled with the economical increase in contractility, the dual action of pimobendan has a favorable hemodynamic effect without an adverse effect on myocardial energy consumption and thus does not appear to further compromise the failing heart. The result has been a reduction in the activity of the neurohormonal compensatory mechanisms as demonstrated in studies in people by reductions in atrial natriuretic peptide, brain natriuretic peptide, norepinephrine, renin, and angiotensin II.[18,19] Additional properties include the reversal of desensitization of baroreceptors,[20] improved lusitropy,[21] reduced platelet aggregation,[c] and an anti-inflammatory effect mediated through cytokine reduction.[22]

Studies and anecdotal reports of the use of pimobendan in Doberman Pinschers with DCM reported improvements in quality and quantity of life when pimobendan was added to traditional therapy[23–25] and this is supported by similar work in humans.[26] Additionally, more recent data from dogs with CHF caused by atrioventricular valvular endocardiosis suggest a benefit with the use of pimobendan.[27,28]

The primary goal of this study was to evaluate the efficacy of pimobendan in improving both the quality and quantity of life in Doberman Pinschers with overt, clinical DCM not complicated by atrial fibrillation while receiving background therapy of furosemide and benazepril hydrochloride.

Materials and Methods

This study was approved by the Animal Care Committee of the University of Guelph with an intended study population of 20 dogs. Owner consent was obtained before enrolling dogs into the study. Doberman Pinschers with confirmed CHF caused by DCM were consecutively enrolled in a prospective, randomized, double-blind, placebo-controlled study. Dogs received background therapy of furosemide[d] (PO as required) and benazepril hydrochloride[e] (0.5 mg/kg PO q12h) and were randomized in pairs and by gender to receive pimobendan[f] (0.25 mg/kg PO q12h) or placebo (1 tablet PO q12h).

Enrollment Criteria

Enrollment was restricted to Doberman Pinschers that were diagnosed with CHF caused by DCM. A definitive diagnosis of CHF caused by DCM was confirmed by radiographic findings of pulmonary edema as well as ventricular dilation and reduced contractility as confirmed by echocardiography (left ventricular internal dimension at end systole [LVIDs] and end diastole [LVIDd] by M-mode of 42 and $\geq$49 mm, respectively, and fractional shortening [FS] by M-mode $<$15%).

Exclusion Criteria

Cardiac criteria precluding study enrollment included concomitant congenital heart disease, evidence of mitral valvular disease (as defined by the morphology of the leaflets on echocardiography), or the presence of atrial fibrillation. Additionally, dogs suffering from concurrent renal disease (serum creatinine concentration $>$3.0 mg/dL and/or urea $>$27.2 mg/dL) or hepatic disease (serum alanine transferase concentration $>$80 U/L and/or alkaline phosphatase $>$300 U/L) or endocrine disease (eg, diabetes mellitus, hyperadrenocorticism) were excluded from study participation.

Study Design

At the time of randomization, an evaluation of history (completion of the QoL assessment), general physical examination, laboratory assessment (CBC and serum biochemical profile), blood pressure assessment (systolic and mean by oscillometry), thoracic radiography, electrocardiography (ECG; standard 9 lead ECG tracing performed with the dogs in right lateral recumbency), echocardiography, and 24 hour ambulatory Holter examination (in-house analysis) were performed on each dog. These data were repeated on a monthly basis until the primary endpoint was met.

From the above, the following variables were examined: QoL variables, temperature, body weight (BW), total daily diuretic dose normalized to BW, systolic (SAP) and mean blood pressure (MAP), serum sodium, hemoglobin concentration, serum urea, serum creatinine, LVIDd, LVIDs, FS, radiographic vertebral heart scale (VHS) score,[26] and ventricular premature beats (VPCs) per hour, pairs of VPCs, triplets of VPCs, and runs of ventricular tachycardia (VT) from the Holter data.

The following calculated values were reported: LVIDd and LVIDs normalized to BW (LVIDd/BW and LVIDs/BW, respectively) and the percent increase in LVIDd (% incr LVIDd) and LVIDs (% incr LVIDs) above predicted normal values. The % incr LVID was calculated as 100$\times$(observed LVID$-$predicted normal LVID)/predicted normal LVID. To determine the predicted normal LVIDd based on BW, the following equation was used: $0.1749\times BW+32.026$.[g] To determine the predicted normal LVIDs based on BW, the following equation was used: $0.1402\times BW+26.723$.[g]

Study End Points

The primary study end point was the time to treatment failure, defined as survival time to death for any reason (including cardiovascular death defined as sudden death, death caused by progressive heart failure, or euthanized for refractory heart failure), or refractory pulmonary edema (requirement of $>$5 mg/kg furosemide PO q8h), whichever occurred first. Dogs that were euthanized for refractory heart failure consisted of cases wherein the owner requested euthanasia before permitting an uptitration of the dose of furosemide to 5 mg/kg q8h. Refractory pulmonary edema was said to occur when an uptitration of furosemide to and including 5 mg/kg q8h failed to resolve clinical signs of respiratory distress and the clinician was compelled to seek greater diuresis. Data were right-censored for dogs that were euthanized for a noncardiac reason, lost to follow-up, or alive at the end of the study.

Secondary end points included total furosemide dose, BW, and the assessment of QoL. For QoL assessment, appetite, attitude, respiratory function, and exercise tolerance were subjectively assessed, as well as recording weight and diuretic dose. A cumulative (total) QoL score was calculated from the above (see the Appendix 1).

Concomitant Treatment

The use of other ACEI or other positive inotropic drugs was not permitted. Other agents were permitted at the discretion of the investigators.

Adverse Drug Reactions

During the study period, any sign possibly attributed to an adverse drug reaction was recorded.

Statistical Analysis

Each of the variables obtained at randomization was assessed for significant difference between treatment groups. For continuous data, an analysis of residuals was performed for each variable within each treatment group to assess normality using a Shapiro-Wilk test. If the *P*-value was $> .1$, we concluded that the data were normal. For data that were not normally distributed, a log transformation was performed and a repeat Shapiro-Wilk test was used to determine whether the data were now normally distributed. For data that were normal or normal after a log transformation, a *t*-test was used to assess significant difference. For data that were not normally distributed, the nonparametric Mann-Whitney–Wilcoxon test was used to assess significant difference between variables by treatment. For data that included a zero and was not normally distributed, a log transformation was not performed and the nonparametric Mann-Whitney–Wilcoxon test was used. For categorical data, a χ^2 test or Fisher's exact test was used.

A log rank test with right censoring was used to determine whether significant difference existed between the 2 treatment groups, and the Kaplan-Meier method was used to estimate the time to treatment failure for each group and plot survival curves.

A univariate Cox proportional hazards test with right censoring was initially performed for each variable to determine whether any baseline variable was associated with the time to treatment failure, and the risk ratio (RR) and 95% confidence limits were calculated. Next, multivariable Cox proportional hazards models, consisting of 2 primary terms (treatment and each other variable) and their interaction, were constructed with right censoring to assess the significance between treatment groups when treatment was modeled with each of the other baseline variables individually.

To determine whether variables remeasured at 1 month differed from baseline values as a result of the treatment group, an analysis of covariance was performed using the baseline variable as the covariate. For data that were not normally distributed, an analysis of covariance could not be performed. For these data the change and percentage change in the variable from baseline were examined. For normal data, including data rendered normal by a log transformation, a *t*-test was performed. For nonnormal data, a Mann-Whitney–Wilcoxon test was used.

Unless otherwise indicated, significance was set at a *P*-value of $< .05$ and all reported values are nominally 2-sided. Caution should be used in the interpretation of findings of statistical significance because no adjustment was made for multiple comparisons.

The statistical analysis was performed using a commercially available statistical software program.[h]

Results

Sixteen dogs (pimobendan treatment group, n = 8; placebo group, n = 8) were enrolled into the study between December 1999 and February 2003. At time of randomization, BW, LVIDs/BW, LVIDd/BW, and MAP were the only variables with a demonstrated difference between treatment groups (see Table 1).

All dogs were receiving furosemide and benazepril at the time of enrollment except 1 dog randomized to pimobendan that was receiving only furosemide. In addition, the following drugs were being administered on the day of enrollment: thyroid (1 pimobendan dog), phenylpropanolamine (1 pimobendan dog), sotalol (1 pimobendan dog, 3 placebo dogs), spironolactone (2 placebo dogs), nitroglycerine (1 pimobendan dog), oxytriphylline (1 pimobendan dog), and prednisone (2 pimobendan dogs, 1 placebo dog). During the course of the trial, the following medications were administered: sotalol (6 pimobendan dogs, 5 placebo dogs) to control ventricular arrhythmias and spironolactone (2 pimobendan dogs, 4 placebo dogs). Additional therapies were administered to treat atrial fibrillation; these are listed in "ECG and Holter Monitor."

Primary End Points

One dog in the pimobendan group failed to reach a cardiac end point (euthanized because of osteosarcoma); all other dogs met the primary study end point (Table 2). Time to treatment failure, as calculated by the log rank test, was statistically significant ($P = .002$) and in favor of pimobendan (median, 130.5 days) over placebo (median, 14 days; Fig 1). Only treatment (use of pimobendan, $P = .003$, RR = 0.35, lower confidence limit [LCL] = 0.13, upper confidence limit [UCL] = 0.71) and body temperature ($P = .02$, RR = 0.36, LCL = 0.15, UCL = 0.84) (higher body temperature) at randomization significantly increased the time to treatment failure using the univariate Cox proportional hazards model with right censoring (Table 3). The relative risk for reaching the end point of treatment failure for the dogs receiving pimobendan was 35% of that for the dogs receiving placebo. When treatment was modeled (multivariable Cox proportional hazards model) with each other variable individually, including the interaction term, treatment continued to significantly affect the time to treatment failure. Only temperature ($P = .02$, RR = 0.37, LCL = 0.13, UCL = 0.85) and diuretic dose/BW/d ($P = .04$, RR = 1.21, LCL = 1.01, UCL = 1.49) had a significant main effect on time to treatment failure when modeled with treatment (Table 4). The interaction term between systolic blood pressure and treatment group, and not systolic blood pressure as a main effect, significantly affected the time to treatment failure (RR for the interaction term = 1.08, LCL = 1.00, UCL = 1.19).

Secondary End Points

For QoL assessment variables (both individual and cumulative scores), none of the variables demonstrated a significant difference at the 1-month evaluation. There were 8 pimobendan dogs and 3 placebo dogs available for analysis at the 1-month time point. BW and diuretic dose normalized for BW (diuretic/BW/d) were not significant at 1 month. At the 2-month time period, 6 pimobendan dogs and 1 placebo dog were available for

Table 1. Demographic and clinical variables on day of enrollment in dogs administered pimobendan or placebo.

	Pimobendan	Placebo	*P*-Value
Number of dogs	8	8	
Sex	6 males 2 females	6 males 2 females	
Age (years)	8.0 (7.8, 10.3)	7.8 (5.8, 9.0)	.19[a]
LVIDd (mm)	54.2 (51.0, 64.4)	61.8 (56.9, 66.7)	.13[a]
LVIDs (mm)	49.7 (46.9, 61.5)	54.7 (52.8, 58.6)	.37[a]
LVIDd/BW (mm/kg)	1.7±0.2	1.5±0.2	.05
LVIDs/BW (mm/kg)	1.5±0.2	1.3±0.1	.02
% incr LVIDd	38.0±0.9	39.3±0.7	.39
% incr LVIDs	31.6±0.2	32.6±0.2	.82
FS (%)	7.4±3.2	10.1±4.6	.21
Na (mEq/L)	148.8±2.3	148.5±3.8	.87
Hb (gm/dL)	16.7±1.7	17.3±1.4	.47
MAP (mmHg)	98.5±14.0[b]	82.9±7.4[c]	.03
SAP (mmHg)	122.9±9.8[b]	115.2±13.0[c]	.24
Urea (mg/dL)	27.2±6.4	26.6±6.2	.87
Creatinine (mg/dL)	0.9±0.4	1.1±0.2	.18
Temperature (°C)	38.5 (38.3,39.3)[c]	38.8 (37.1,39.1)	.64[a]
BW (kg)	34.4±5.1	41.8±3.8	.01
VPCs (per hour)	179.9±366.3	187.6±287.8[c]	.61
Diuretic/BW/d	9.6±4.5	7.2±3.8	.26
VHS	11.4±0.6	11.8±0.9	.28
Appetite score (0–3)	0.2 (0.0,0.9)	1.0 (0.0,1.5)	.38[a]
Attitude score (0–4)	0.8±0.8	0.8±0.8	.87
Resp Ftn score (0–3)	1.5 (1.0,2.0)	0.8 (0.0,1.5)	.18[a]
Stamina score (0–3)	1.5 (1.0,2.0)	1.0 (0.2,1.5)	.10[a]
Total score (0–13)	4.2±2.0	3.4±2.4	.51
Sotalol	6	5	
Spironolactone	4	4	

Data are presented as mean±standard deviation, except for those with the superscript (a), which are presented as median (lower quartile,upper quartile).

[a]*P*-value determined by the nonparametric Mann-Whitney–Wilcoxon test; all other *P*-values determined by a *t*-test.

[b]Determined on 6 dogs.

[c]Determined on 7 dogs.

LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; % incr, percent increase measured as described in "Materials and Methods"; FS, fractional shortening; Na, serum sodium; Hb, hemoglobin; MAP, mean arterial pressure; SAP, systolic arterial pressures; BW, body weight; VPCs, ventricular premature contractions; VHS, vertebral heart scale; score 0 refers to normal and 4 refers to most adversely affected; resp ftn, respiratory function.

assessment. This precluded the analysis of QoL variables at the 2-month time point.

ECG and Holter Monitor

Atrial fibrillation developed in 6 dogs (pimobendan group, n = 4; placebo group, n = 2). There is no significant difference between the incidence of atrial fibrillation in each treatment group. Time to treatment failure after the onset of atrial fibrillation was 4.7 days with a range of 0–9 days. Therapy for atrial fibrillation consisted of sotalol (1 dog), metoprolol (2), diltiazem (1) in the pimobendan dogs, and sotalol (1) in the placebo dogs.

Table 2. Outcome of dogs.

	Pimobendan	Placebo
Treatment failure	7	8
Furosemide failure[a]	3	5
Sudden death	3	1
Death caused by congestive heart failure (CHF)	0	0
Euthanasia because of CHF	1	2
Death caused by noncardiac causes[b]	1	0
Developed atrial fibrillation	4	2

[a]The inability of furosemide to control respiratory signs of pulmonary edema at doses >5 mg/kg q8h.

[b]Death before treatment failure attributable to osteosarcoma.

One placebo dog was diagnosed with atrial fibrillation on the treatment failure date.

Data were available for 6 pimobendan dogs and 1 placebo dog to assess change in the frequency of VPCs per hour at 1 month. The mean percentage change in VPCs per hour for the pimobendan dogs at 1 month was a reduction of 1072% with a range of 5363 to −94%. There was no change in the frequency of pairs of VPCs per hour and triplets of VPCs per hour within the pimobendan group when baseline was compared with the 1-month Holter examination. Within the pimobendan group, there was 1 run of nonsustained VT in 1 dog on the day of randomization and there were 4 dogs with nonsustained VT at the 1-month exam. Two dogs had 1 run each, 1 dog had 2 runs, and 1 dog had 4 runs of nonsustained VT at the 1-month Holter examination. The placebo dog had 6.14 and 16.54 VPCs/h at 0 and 1 month, respectively; 0.14 and 0 pairs/h; 0.05 and 0.13 triplets/h; and 0 runs of VT and 0 runs of VT, respectively.

Adverse Drug Reactions

There were no adverse drug reactions reported.

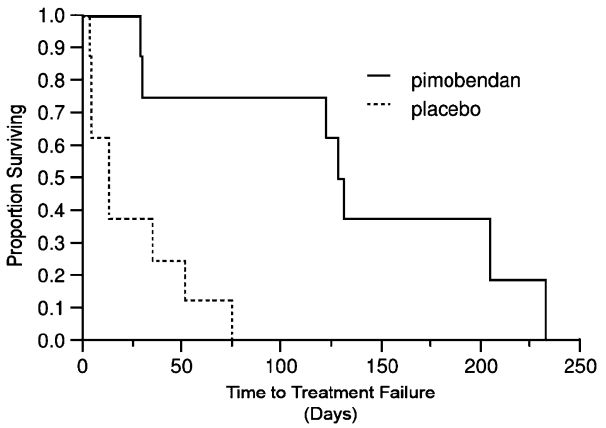

Fig 1. Censored time to treatment failure results: median survival for the pimobendan treated dogs (n = 7) was 130.5 days versus the placebo dogs (n = 8) 14 days ($P = .002$; relative risk, 0.35; confidence interval, 0.13–0.71).

Table 3. A univariate analysis of variables that influenced time to treatment failure using a Cox proportionate hazards model with right censoring.

Parameter	*P*-Value	Risk Ratio (CL)
Treatment (Pimo)	.003	0.35 (0.13–0.71)
Sex (female)	.69	1.12 (0.59–1.99)
Age (years)	.58	0.94 (0.73–1.16)
LVIDd (mm)	.27	1.05 (0.96–1.14)
LVIDs (mm)	.44	1.03 (0.95–1.12)
FS (%)	.67	1.03 (0.89–1.19)
LVIDd/BW (mm/kg)	.62	0.44 (0.02–11.75)
LVIDs/BW (mm/kg)	.54	0.38 (0.01–8.36)
% incr LVIDd	.33	1.02 (0.98–1.06)
% incr LVIDs	.55	1.00 (0.98–1.04)
Na (mEq/L)	1.00	1.00 (0.83–1.21)
Hb (gm/dL)	.59	0.99 (0.96–1.02)
MAP (mmHg)	.55	0.99 (0.94–1.03)
SAP (mmHg)	.40	0.97 (0.91–1.03)
Urea (mg/dL)	.98	1.00 (0.80–1.28)
Creatinine (mg/dL)	.38	1.01 (0.99–1.03)
Temperature (°C)	.02	0.36 (0.15–0.84)
BW (kg)	.18	1.07 (0.97–1.19)
VPCs (per hour)	.97	1.00 (1.00–1.00)
Diuretic/BW/day (mg/kg/d)	.62	1.04 (0.90–1.20)
VHS	.85	1.08 (0.45–2.45)
Beta blocker	.87	1.05 (0.55–1.85)
Spironolactone	.76	0.92 (0.53–1.68)
Appetite at rand	.98	1.01 (0.44–2.08)
Attitude at rand	.90	1.05 (0.50–2.08)
Resp Ftn at rand	.30	0.72 (0.38–1.36)
Stamina at rand	.47	0.75 (0.33–1.66)
Total score at rand	.57	0.93 (0.72–1.19)

CL, confidence limit (5–95%); LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; % incr, percent increase measured as described in "Materials and Methods"; FS, fractional shortening; Na, serum sodium; Hb, hemoglobin; MAP, mean arterial pressure; SAP, systolic arterial pressure; BW, body weight; VPCs, ventricular premature contractions; diuretic/BW/d, diuretic dose/body weight/day; VHS, vertebral heart scale; appetite at rand, appetite score at randomization; attitude at rand, attitude score at randomization; resp ftn, respiratory function score at randomization; stamina at rand, stamina score at randomization.

Discussion

This study of a small number of dogs demonstrates that the addition of pimobendan to traditional therapy consisting of a diuretic and ACEI significantly increases survival in Doberman Pinschers with CHF caused by DCM.

Because an interim analysis demonstrated a >5-fold increase in the mean time to treatment failure and a 65% reduction in the risk of developing treatment failure with the use of pimobendan, we considered it unethical to continue the study and elected to end the study before the intended goal of enrolling 20 dogs.

The results of this study are in agreement with previously reported data of pimobendan use in dogs with CHF caused by DCM. In 10 Doberman Pinschers with overt DCM and on a background therapy of furosemide, enalapril, and digoxin that were randomly assigned to receive either pimobendan or placebo, all pimobendan-treated dogs had improvement in QoL (assessed via changes in New York Heart Association disease classification) and the median survival was 50 days for the placebo group versus 329 days for the pimobendan group.[23] However, a study limitation (despite randomization) was a disproportionate number of dogs in the placebo group with atrial fibrillation (3 of 5 pimobendan dogs versus 1 of 5 placebo dogs) at the onset of the study. Earlier work suggests that atrial fibrillation in Doberman Pinschers with CHF caused by DCM confers a marked reduction in survival despite traditional therapy.[6,a] Nevertheless, the Fuentes study and the current study remain the only studies to date to demonstrate that any therapeutic intervention significantly increased survival in dogs with CHF caused by DCM.

The current study failed to demonstrate a significant improvement in QoL assessment, unlike the Fuentes study.[23] The current study was hampered by the failure of dogs within the placebo group to remain free of treatment failure by the 1st and 2nd month time points. Only 3 placebo dogs were available for analysis at the 1-month point and 1 placebo dog was available at the 2-month point. Nevertheless, as more placebo dogs reached treatment failure during the 1st and 2nd month than the pimobendan dogs, it is our opinion that QoL must have been more adversely affected in the placebo dogs during this same time period.

An assessment of randomization indicated a disparity between study groups at time 0; the pimobendan group had greater cardiac enlargement at study enrollment based on significantly greater echocardiographic ventricular dimensions normalized for BW. Cardiac enlargement

Table 4. Effect of treatment when modeled with each variable using a multivariable Cox proportional hazards analysis.

Significant Variables Modeled with Treatment	Variable	*P*-Value	Risk Ratio (CL)
Temperature (°C)	Treatment	.006	0.35 (0.13–0.75)
	Temperature	.02	0.37 (0.13–0.85)
	Interaction term	NS	
Diuretic/BW/day (mg/kg/d)	Treatment	.0003	0.22 (0.07–0.53)
	Diuretic/BW/day	.04	1.21 (1.01–1.49)
	Interaction term	NS	
SAP (mmHg)	Treatment	.0003	0.11 (0.02–0.42)
	SAP	.83	
	Interaction term	.04	1.08 (1.00–1.19)

CL, confidence limit (5–95%); BW, body weight; diuretic/BW/d, diuretic dose/BW/day; SAP, systolic arterial pressure; NS, not significant.

is a recognized poor prognostic indicator in humans with heart failure.[30] Despite the fact that the pimobendan group may have had more advanced heart failure at the onset of the trial, the time to treatment failure was still significantly greater for the pimobendan group. In addition, when treatment was modeled with LVIDd/BW and LVIDs/BW, treatment continued to significantly affect the outcome after adjusting for these variables. Neither of these variables affected outcome in either the univariate or multivariable models.

The current study investigated whether any of the variables, including treatment, individually had an effect on the time to treatment failure (Table 3). Only temperature, in addition to treatment, was associated with a significant effect on time to treatment failure. Reduced temperature is likely related to a lower cardiac output, which is a recognized poor prognostic indicator in humans with CHF.[30] Analyses attempted to further determine whether the beneficial effect of treatment might be confounded by another variable. Cox proportional hazards modeling with treatment and each of the other variables individually, including the interaction term, demonstrated that treatment continued to be significantly associated with time to treatment failure. A lower temperature and greater diuretic requirement also significantly reduced the time to treatment failure when each was modeled with treatment (Table 4). The need for a higher diuretic dose suggests more advanced heart failure, which is also an important prognostic indicator in humans with heart failure.[30] The multivariable modeling also demonstrated that the benefit of pimobendan treatment either increased (when modeled with systolic arterial pressure [RR = 0.11] or diuretic dose/BW/d [RR = 0.22]) or remained unchanged (when modeled with temperature [RR = 0.35]) when compared with placebo therapy (Table 4). And finally, we examined the effect of modeling treatment with both temperature and diuretic dose normalized to BW. In this analysis, diuretic dose was not significant as a main effect; temperature and treatment continued to be significant.

It is worth noting that the failure to demonstrate an effect on outcome by many of the variables studied is in contrast to human studies where most have been demonstrated to have a significant effect on outcome. This is most likely a result of a small effect of the variable combined with the small sample size. To demonstrate a relatively small statistical effect usually requires a large sample. A variable having a significant effect within a small sample indicates that the magnitude of the effect must by necessity be profound. This is the case with the effect of pimobendan on time to treatment failure in this study.

Preliminary data on pure PDE III inhibitors in human medicine indicated that, despite improvements in morbidity, they significantly increased mortality (likely attributable to arrhythmogenesis), resulting in study termination and pre-empting their market availability.[31] Similar concerns have been raised regarding the use of these products in veterinary medicine; however, early product withdrawal precluded an assessment of their impact on morbidity and mortality in animals. Pimobendan has been evaluated for its arrhythmogenic potential in humans. Although an early study suggested a potential increased risk with pimobendan use,[32] a subsequent study did not.[26] This agrees with a recently published study of pimobendan use in dogs with CHF caused by mitral valve endocardiosis where the pimobendan group failed to show an increase in ventricular arrhythmias.[27] The present study also failed to demonstrate a significant increase in the VPCs per hour, pairs of VPCs per hour, and triplets of VPCs per hour in the pimobendan group at 1 month when compared with their baseline values. There was an increase in the number of nonsustained runs of VT over the study in the pimobendan group. There was also an increase in the incidence of sudden death in the pimobendan dogs (3) as compared with the placebo dogs (1). The small numbers of patients involved, however, prevents a determination of whether this increase in numbers of patients with nonsustained VT and sudden death is due to pimobendan or a product of a longer survival. There were twice as many dogs that developed atrial fibrillation in the pimobendan group; this was not statistically significant. However, this analysis fails to account for the effect of increased survival on the likelihood of developing atrial fibrillation. Overall, the potential to promote arrhythmias is an important concern with positive inotropes, including pimobendan, and further studies are needed to further explore this issue, particularly in dogs at high risk of arrhythmias.

In this study, no other adverse events occurred that could be ascribed to pimobendan therapy.

As with any study, this study has limitations, including small sample size and relatively long reassessment intervals making QoL comparisons between groups difficult. The latter issue would have been partially overcome by using shorter time intervals between scheduled reassessments providing for greater number of patients at each time point. With regard to sample size, although the overall study population was small, the results were statistically significant and clearly visible between groups; statistical significance derived from small study numbers is indicative of findings with marked clinical significance. This result is consistent with the earlier work with Doberman Pinschers with CHF caused by DCM.[23]

In 1 dog in the current study, the blinding protocol was compromised and the clinician was inadvertently informed of treatment allocation. This 1 occasion did not result in an end-point allocation, and the dog continued in the study with the investigators blinded on all subsequent examinations.

The time to treatment failure included pulmonary edema refractory to furosemide at 5 mg/kg q8h. This end point is not survival but a surrogate for survival. It remains to be determined how effective refractoriness to furosemide is as a surrogate for survival in CHF. In addition, Doberman Pinschers were studied as opposed to a study sample consisting of many breeds with DCM. Dobermans with CHF and DCM have a shorter survival compared with other breeds.[a] It remains to be demonstrated whether other breeds would also respond like this Doberman Pinscher sample.

The use of multivariable modeling in the Cox proportional hazards analyses is dependent on the number of patients that reach the noncensored end point. It has been suggested that 10 patients that achieve a noncen-

sored event are required for each variable in a multivariable analysis.[33] We believe this is too conservative and have examined 3 term models. Too many terms in a model can result in overfitting of the model.[33] In addition, there are more than 100 potential models that can be examined in 3 term models with the number of variables available in our study. We selected to examine a small list of potential models. We did, however, examine all potential 2-term models involving treatment and the interaction term with treatment.

Conclusions

The results of this study demonstrate that the addition of pimobendan to the treatment of CHF attributable to DCM in Doberman Pinschers provides a profound advantage over traditional therapy of a diuretic and ACEI in reducing mortality. The results clearly support pimobendan use as a first-line therapeutic, once CHF has been diagnosed. Studies in a larger sample of dogs of various breeds with CHF caused by DCM would be important.

Footnotes

[a] Bronsoiler J, O'Grady MR, Minors SL, O'Sullivan ML. Dilated cardiomyopathy in dogs with congestive heart failure: Prognostic factors and influence of atrial fibrillation on survival. J Vet Intern Med 2005;19:456 (abstract)

[b] O'Grady MR, Horne R, Gordon SG. Does angiotensin converting enzyme inhibitor therapy delay the onset of congestive heart failure or sudden death in Doberman Pinschers with occult dilated cardiomyopathy? J Vet Int Med 1997;11:138 (abstract)

[c] Bastida E, Escolar G, Rodriguez-Gomez J, et al. UD-CG 115, a benzimidazole-pyridazinone compound with cardiovascular activity inhibits platelet thrombus formation. Thromb Res 1986; 42, (Suppl 6): 145 (abstract)

[d] Apo-furosemide, Apotex Inc, Weston, ON, Canada

[e] Fortekor, Novartis Animal Health, Mississauga, ON, Canada

[f] Vetmedin, Boehringer Ingelheim Canada Ltd, Burlington, ON, Canada

[g] M.R. O'Grady, unpublished data in normal Doberman Pinschers; Guelph, ON

[h] JMP version 4.0.2; SAS Institute Inc, Cary, NC

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Appendix 1. Quality of life variable scoring

1. Attitude (alertness) and behavior (demeanor)

Normal activity, alert and responsive. Attitude compared with that of 2 years ago	0
Alertness mildly depressed or subdued. Reacts rapidly to external stimuli. Minimal coaxing required	1
Level of alertness moderately depressed. Slow response to stimuli, will stand up and move with moderate encouragement	2
Minimal level of activity, responds to stimuli around it with difficulty, will get up or move only with significant encouragement	3
Very depressed, almost unresponsive to external stimuli, will not move unless forced to move	4

2. Exercise capacity

Normal activity, stamina, and exercise capacity. Stamina comparable to that of 2 years ago	0
Tires with heavy exercise	1
Tires with minimal exercise (walking up steps, cannot walk around the block without tiring)	2
Reluctant to move about at all because of lack of stamina	3

3. Respiratory function

Normal (rate, depth, absence of cough or wheeze). Respiration comparable to that of 2 years ago	0
Mild dyspnea (increased rate and/or depth). Dyspnea or wheezing associated with heavy exercise, or infrequent cough	1
Moderate dyspnea or wheezing with light exercise. Frequent cough, particularly at night	2
Severe dyspnea; usually dyspneic or wheeze at rest, coughing is frequent or orthopnea is common (lays or sleeps in sternal recumbency)	3

4. Appetite

Normal appetite, comparable with that of 2 years ago	0
Slightly reduced appetite	1
Moderately reduced, requires lots of coaxing	2
Severely reduced or completely absent	3

5. Overall owner assessment

Markedly worse		Slightly improved
Moderately worse	No change	Moderately improved
Slightly worse		Markedly improved