

Efficacy and safety of pimobendan in canine heart failure caused by myxomatous mitral valve disease

OBJECTIVES: To evaluate the clinical efficacy and safety of pimobendan by comparing it with ramipril over a six-month period in dogs with mild to moderate heart failure (HF) caused by myxomatous mitral valve disease (MMVD).

METHODS: This was a prospective randomised, single-blind, parallel-group trial. Client-owned dogs (n=43) with mild to moderate HF caused by MMVD were randomly assigned to one of two groups, which received either pimobendan (P dogs) or ramipril (R dogs) for six months. The outcome measures studied were: adverse HF outcome, defined as failure to complete the trial as a direct consequence of HF; maximum furosemide dose (mg/kg/day) administered during the study period; and any requirement for additional visits to the clinic as a direct consequence of HF.

RESULTS: Treatment with pimobendan was well tolerated compared with treatment with ramipril. P dogs were 25 per cent as likely as R dogs to have an adverse HF outcome (odds ratio 4.09, 95 per cent confidence interval 1.03 to 16.3, P=0.046).

CLINICAL SIGNIFICANCE: R dogs had a higher overall score and thus may have had more advanced disease than P dogs at baseline (P=0.04). These results should be interpreted cautiously but such a high odds ratio warrants further investigation.

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INTRODUCTION

Myxomatous mitral valve disease (MMVD) is a common cause of heart failure (HF) in dogs, and the addition of an angiotensin-converting enzyme (ACE) inhibitor to standard therapy has been demonstrated to be efficacious and safe in this setting (COVE Study Group 1995, IMPROVE Study Group 1995, LIVE Study Group 1998, BENCH Study Group 1999).

A reduction in preload and afterload through venous and arteriolar dilation, respectively, is considered to be desirable in dogs with HF caused by MMVD. In contrast, because MMVD is not obviously accompanied by an impairment of contractility in most cases, the use of a pharmacological agent with a positive inotropic effect is controversial. However, in addition to severe valvular insufficiency, there is evidence to suggest that an impairment of contractility also contributes to the development of HF in dogs with MMVD (Kittleson and others 1984, Urabe and others 1992, Lord and others 2003). Wall motion in dogs with mitral regurgitation is greatly augmented by an increased preload and reduced afterload, therefore masking the effects of a depressed inotropic state on the pumping function of the heart (Eckberg and others 1973). Increased sympathetic nervous system activity may also obscure the intrinsic decline in myocardial contractility in dogs with advanced MMVD (Nagatsu and others 1994).

Pimobendan (4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]-5-methyl-3(2H)-pyridazinone) is a benzimidazole derivative with combined inotropic and peripheral vasodilating (inodilating) properties (Takahashi and Endoh 2001). Benzimidazole derivatives exert inotropic effects through a combination of inhibiting phosphodiesterase (PDE) III and sensitising cardiac myofilaments to intracellular calcium, and for this reason are commonly termed calcium sensitising agents (Fitton and Brogden 1994).

Pimobendan may additionally mediate increases in cyclic adenosine monophosphate (cAMP) accumulation by mechanisms other than PDE III inhibition, including A₁-adenosine receptor antagonism and inhibition of G_i function (Parsons and others 1988). Inhibition of PDE III and PDE V produces both venous and arteriolar dilation (Mathew and Katz 1998).

Pimobendan appears to be well tolerated at therapeutic doses in humans with chronic HF and preliminary indications suggest that, in addition to contributing to a consistent improvement in exercise capacity and quality of life, it is largely devoid of the proarrhythmic effects of classical PDE III inhibitors (Erlemeier and others 1991, Fitton and Brogden 1994). Although early clinical trial data demonstrated a trend towards increased mortality in patients treated with pimobendan (PICO Investigators 1996), a recent study demonstrated a reduction in the incidence of adverse cardiac events, including worsening of HF and a decrease in functional capacity, without a significant effect on mortality in patients with mild to moderate congestive HF (EPOCH Study Group 2002). Patients enrolled into the clinical trials had predominantly ischaemic heart disease or dilated cardiomyopathy, and it is unknown whether or not similar results would be found in patients with valvular heart disease.

Studies of pimobendan treatment in dogs with congestive HF caused by dilated cardiomyopathy also demonstrate a consistent improvement in functional HF class (Lombard 2000, Luis Fuentes and others 2002) and, in the case of dobermanns, an improvement in survival (Luis Fuentes and others 2002). However, there are no published studies that have exclusively evaluated the efficacy and safety of pimobendan in dogs with MMVD. Therefore its efficacy in dogs with congestive HF caused by MMVD remains unknown, and its potential role warrants further investigation.

The aim of the present study was to compare the clinical efficacy and safety of pimobendan (Vetmedin; Boehringer

Ingelheim) with ramipril (Vasotop; Intervet) over a six-month period in dogs with mild to moderate HF caused by MMVD.

MATERIALS AND METHODS

The present study was a prospective randomised, single-blind, parallel-group trial. It was conducted at the Royal (Dick) School of Veterinary Studies, the Scarsdale Veterinary Hospital and the Cheadle Hulme Veterinary Hospital in the UK.

Inclusion criteria

The inclusion criteria were that dogs must have class II to III left-sided HF caused by MMVD, in accordance with the New York Heart Association (NYHA) system modified by Kvart and others (2002). Dogs without clinical signs of left-sided congestive HF (class II) were only suitable for enrolment if they were receiving treatment for HF, and it was thought that they would be in class III or IV HF following withdrawal of the treatment. Diagnosis and suitability for enrolment were based on medical history, ongoing clinical signs and a clinical examination, and were confirmed by a combination of electrocardiography, thoracic radiography and echocardiography.

Exclusion criteria

Animals were excluded from entry to the study if they had renal and/or hepatic disease, or other debilitating disorders that can affect evaluation of response to cardiac treatment. Dogs being treated with furosemide and/or digoxin at the initial evaluation were potentially eligible for enrolment. Current or prior treatment for HF with a vasodilator and/or inodilator was only permitted in exceptional circumstances (treatment was not prolonged and medication had been withdrawn for more than seven days).

Study design

A preliminary case evaluation was performed one to two weeks prior to the anticipated time of randomisation into the

study. Following stabilisation of HF (including the elimination of radiographic evidence of interstitial oedema) with furosemide plus or minus digoxin, and baseline evaluation, dogs meeting the inclusion criteria were randomly assigned to receive either pimobendan or ramipril in a single-blind fashion for six months. The attending veterinary surgeons were blinded as to the treatment group of each dog.

Treatment allocation

Within each study location, dogs were paired based on order of admission to the study. Separate allocation schedules consisting of pimobendan and ramipril couplets, where one dog from each couplet received pimobendan and the other received ramipril, were established in a random fashion for each location prior to the study commencing.

Treatment

The target dose for pimobendan was 0.3 mg/kg, every 12 hours orally. The target dose for ramipril was 0.125 mg/kg, every 24 hours orally. However, tablets could be divided only once to achieve a dose as close to, but not less than, 0.125 mg/kg every 24 hours.

All dogs were also treated with furosemide (Frusemide Tablets BP; Millpledge Pharmaceuticals). The minimum effective dose of furosemide was prescribed at all times and was reassessed at each visit. The operators were also able to prescribe digoxin for the treatment of supraventricular tachyarrhythmias. No concomitant treatment with other inodilator drugs, other ACE inhibitors or vasodilators was permitted.

Evaluation schedule

All dogs meeting the inclusion criteria at baseline were scheduled for re-evaluation after one, three and six months. Dogs were evaluated at each scheduled visit with a patient history, clinical examination, quality of life questionnaire, electrocardiographic examination for five minutes, right

Table 1. Scoring system used for clinical examination and quality of life questionnaire variables

Cough scores*†	Respiratory effort†	Appetite*	Demeanour†	Mobility*	Attitude*	Activity*
0 None	0 Normal	1 Increased	0 Alert, responsive	1 Very good: walks well, runs, capable of some strenuous activity	1 Increased: has stronger desire and interest than in the past to go out for walks or play with owner. Appears more alert and responsive to surrounding environment	1 High: moves around with ease, capable of climbing stairs or running short distances. Alert and responsive to external stimuli
1 Occasional	1 Mildly increased effort	2 Normal	1 Mildly depressed	2 Good: walks well, will run a short distance or pulls on lead but unable to do strenuous activity, tires easily after walking one to two blocks	2 Remained the same: has approximately the same degree of interest and desire to go out for walks or play with owner as in the past, is as alert to the surrounding environment as before	2 Moderate: tends to be inactive, but moves around a few times per day. Has difficulty with stairs and long walks
2 Frequent	2 Laboured	3 Decreased	2 Moderately depressed	3 Moderate: will walk, but for a limited distance before needing to rest	3 Decreased: has some interest, but plays less often, and has decreased interest in going for a run or walk	3 Low: generally inactive, tendency to remain in one place most of the day and is unable to climb stairs or walk more than a short distance
3 Persistent	3 Respiratory distress	4 Markedly decreased	3 Minimally responsive	4 Poor: can only walk a few metres before needing to rest 5 Very poor: to get up and move is a major effort, only able to move a few steps before resting		4 Minimal: remains inactive all day and only gets up to eat, drink or urinate 5 Incapacitated: will only get up or move if strongly encouraged by owner

*Scores obtained from the quality of life questionnaire

†Scores obtained from the clinical examination

‡A 'total cough score' was derived from the sum of three separate cough scores (at night, during normal activity and during exercise)

lateral and dorsoventral thoracic radiography, and echocardiography. Additionally, indirect systolic blood pressure, routine urinalysis and serum biochemistry (including serum total thyroxine [T₄]) were evaluated at baseline at one and six months. Full haematology was evaluated at baseline and six months. Only those tests deemed necessary for the provision of optimal treatment were performed at additional visits. If a dog was euthanased, died or was withdrawn from the study prior to completion, the date and reason were recorded.

Clinical evaluation

In order to evaluate the clinical efficacy of HF therapy objectively from the clinical examination and quality of life questionnaire, specific categories, the same as those used by the IMPROVE Study Group (1995), were established and assigned a score (Table 1). Other variables recorded at clinical examination included heart rate, respiratory rate and bodyweight. All laboratory tests were performed by the University of Edinburgh's clinical laboratory.

A standard six-lead electrocardiogram (ECG) was recorded for a period of five minutes in order to determine the presence or absence of ventricular and/or supraventricular premature complexes. Thoracic radiographs were obtained at each of the scheduled visits in order to optimise diuretic dose and to monitor disease progression. Indirect systolic blood pressure measurement was performed using an ultrasonic Doppler flow detector. Either the left or right forelimb's metacarpal artery was used, with the paw held at heart level. The initial measurement was discarded, and systolic blood pressure was determined as the mean of at least five subsequent readings.

Echocardiography

A range of echocardiographic variables was measured or calculated at baseline (Table 2).

Two-dimensional and M-mode, and Doppler echocardiographic examinations were performed using a 5.0 and 2.5 MHz transducer, respectively. Five measure-

ments were attempted for each variable and the average value was used in the statistical analysis. A simultaneous ECG was recorded for all the images. Unless stated otherwise, diastolic events were timed from the ECG as the start of the QRS complex and systolic events were timed from the ECG as the end of the T wave, or using the mechanical phase of the scan itself. Two-dimensional and M-mode echocardiographic variables were obtained following the standards advocated by the American Society for Echocardiography and the Joint International Society and Federation of Cardiology/World Health Organization Task Force, respectively (O'Rourke and others 1984, Thomas and others 1993).

The left ventricular (LV) volumes at end diastole (LV_{vol} [dl]) and end systole (LV_{vol} [s]) were derived from images recorded from a four-chamber, right parasternal, long-axis view, in which the length and width of the LV chamber had been maximised at end diastole and end systole, respectively. For these measure-

Table 2. Doppler and echocardiographic variables measured or calculated and analysed in the study

Abbreviation	Units	Description	Abbreviation	Units	Description
LV _{vol} (d)	cm ³	Left ventricular volume at end diastole	$\frac{2D-Ao_d(d)}{2D-LA_d(d)}$		Calculated ratio
LV _{vol} (s)	cm ³	Left ventricular volume at end systole	Ao VT _i	cm	Subcostal aortic velocity time integral
LVd	cm	Left ventricular diameter during diastole (M-mode)	Ao V _{max}	m/second	Subcostal aortic velocity
LVs	cm	Left ventricular diameter during systole (M-mode)	$\frac{dv}{dt}$	m/second ²	Mean rate of change of aortic blood flow velocity
FS percentage	%	Fractional shortening	PEP	second	Pre-ejection period (derived from pulsed wave Doppler recording of aortic velocity curve from a subcostal position)
EPSS	cm	Mitral E point to septal separation	LVET	second	Left ventricular ejection time (derived from the same frame as the PEP)
2D-Ao _d (d)	cm	Internal short-axis diameter of the aorta along the commissure between the non-coronary and left coronary aortic valve cusps during diastole	$\frac{PEP}{LVET}$		Calculated ratio
2D-LA _d (d)	cm	Internal short-axis diameter of the left atrium in the same frame as 2D-Ao _d (d) ¹⁵	RF percentage	%	Mitral regurgitant fraction
Ao diam	cm	Internal diameter of the aorta during systole, measured at the sinotubular junction from the long-axis LV outflow tract view from the left parasternal location	MR V _{max}	m/second	Peak mitral regurgitant blood flow velocity recorded from the left parasternal location

ments, end diastole was defined as the largest LV dimension just before mitral valve closure and end systole was defined as the smallest LV dimension just before mitral valve opening (Schiller 1991, Schiller and Foster 1996). The LV_{vol} (d) and LV_{vol} (s) were subsequently calculated using the modified Simpson's formula (Schiller and others 1989). Left ventricular length was measured from the left ventricular apex to the midpoint of a straight line connecting the hinge points of the anterior and posterior mitral valve leaflets.

The RF percentage is the mitral regurgitant stroke volume expressed as a percentage of the overall LV stroke volume. The mitral regurgitant stroke volume used to calculate the RF percentage was calculated by subtracting the aortic stroke volume (aortic velocity time integral [Ao VT_i] × cross-sectional area of aorta [(Ao diam)² × 0.785]) from the total LV stroke volume (LV_{vol} [d] – LV_{vol} [s]).

Outcome measures

The primary outcome measure was the occurrence of an adverse HF outcome. This was defined as failure to complete the trial; in other words, the dog was euthanased, died or discontinued the trial, as a direct consequence of HF. Secondary outcome measures were the maximum furosemide dose (mg/kg/day) administered during the study period and the requirement for additional visits to the clinic as a direct consequence of HF.

Endpoints

Endpoints used to assess the efficacy and

safety of therapy during the study period were clinical examination and quality of life questionnaire scores (cough, respiratory effort, appetite, demeanour, mobility, attitude, activity and overall scores), heart rate, blood pressure, the occurrence of ventricular premature complexes (VPCs) and/or supraventricular premature complexes (SPCs), the occurrence of adverse events not leading to withdrawal from the study, and abnormal haematological and/or serum biochemical findings.

Statistical analysis

Two groups were compared using the chi-squared test or Fisher's exact test for proportions, and the Mann-Whitney U test for continuous or ordinal categorical variables. The means are presented rather than the medians because the medians and lower and upper quartiles are generally the same for the different groups, and are not useful for comparison purposes.

Baseline characteristics of the two treatment groups were compared to assess the level of balance between the two groups, and the impact of each variable was considered separately to determine its influence on the outcome measures. Logistic regression was used to assess which variables predicted the occurrence of an adverse HF outcome and additional clinic visits. Linear regression was used to assess which variables predicted maximum furosemide dose. Due to the relatively small sample size and the number of variables, it was considered better to examine these factors in separate models rather than examining them simultaneously in a single

model. The odds ratios (ORs) are given for the logistic regression and the parameter estimates are given for the linear regression analysis. The increased or decreased odds can be considered to be an assessment of the increased or decreased risk.

The baseline predictors considered were as follows: study medication (pimobendan or ramipril), sex, age, location, clinical signs present at initial evaluation (Table 3), medication received at or prior to enrolment into the study (Table 3), bodyweight, quality of life questionnaire and clinical examination scores and variables, blood pressure, ECG variables (heart rate, rhythm, presence of ectopic complexes [SPC/VPC], P-R duration, QRS duration, R wave amplitude and Q-T duration), echocardiographic variables (Table 2), and data derived from full haematology, serum biochemistry and urinalysis. However, the primary analysis was to compare the percentage of dogs with an adverse HF outcome between the two treatment groups. Since treatment allocation in the study was randomised, it was not recommended that the analysis be adjusted for baseline factors (Kirkwood and Sterne 2003).

A repeated measures analysis (using a compound symmetry covariance structure) was performed to assess the effect over time on the following variables: the quality of life questionnaire and clinical examination scores, blood pressure, heart rate and presence of premature complexes (SPC and VPC). The baseline level of the continuous variables was entered into the model as a covariate. For all analyses, values of P<0.05 were considered significant.

Table 3. Baseline characteristics by randomisation

Baseline characteristics		Pimobendan	Ramipril	P value
Basic characteristics	Cavalier King Charles spaniel	55%	62%	0.86†
	Age (years)	Mean 10.4	Mean 9.8	0.37‡
	Bodyweight (kg)	Mean 12.5	Mean 11.7	0.81‡
	Male	55%	67%	0.62†
	Neutered	55%	33%	0.27†
	Centre	45% location 1, 14% location 2, 41% location 3	42.8% location 1, 9.5% location 2, 47.6% location 3	0.75†
Clinical signs present at initial evaluation	Cough	91%	100%	0.49†
	Collapse	14%	29%	0.41†
	Exercise intolerance	59%	76%	0.38†
	Exertion-induced dyspnoea	55%	71%	0.41†
	Dyspnoea at rest	50%	33%	0.43†
	Other health problems	23%	33%	0.66†
Medication received prior to enrolment into the study	Receiving furosemide	32%	48%	0.46†
	Baseline furosemide dose (mg/kg/day)	Median 3.44, quartiles 2.33 and 4.17	Median 3.85, quartiles 2.27 and 6.67	0.33‡
	Receiving ACE inhibitors	9%	5%	1.00†
	Receiving pimobendan	9%	5%	1.00†
	Receiving digoxin	0%	0%	
	Receiving other drugs	0%	5%	0.49†
Recorded clinical scores at baseline	Appetite	Mean 2.14	Mean 2.24	0.64‡
	Mobility	Mean 1.91	Mean 2.53	0.04‡
	Attitude	Mean 2.05	Mean 2.1	0.70‡
	Activity at home	Mean 1.32	Mean 1.76	0.14‡
	Total cough score	Mean 2.45	Mean 3.29	0.22‡
	Demeanour*	5% score ≥1	40% score ≥1	0.01†
	Respiratory effort*	32% score ≥1	43% score ≥1	0.67†
	Overall score	Mean 10.2	Mean 12.5	0.04‡

Bold text denotes statistically significant results

ACE Angiotensin-converting enzyme

*A significance test based on the comparison of means would not be appropriate due to the small number of categories and spread of data over the categories

†Chi-squared test or Fisher's exact test

‡Mann-Whitney U test

Overall score: the sum of all the scores above

RESULTS

Between December 2000 and August 2002 a total of 44 dogs were enrolled. One dog was accidentally administered a dose of less than 0.125 mg/kg/day ramipril, which led to its exclusion from the statistical analysis. Of the dogs analysed, 22 were randomised to pimobendan and 21 to ramipril.

Baseline characteristics

Twenty-six (60 per cent) of the dogs were male and 17 (40 per cent) were female. The mean (se) age of the dogs was 10.1 (0.39) years. The majority of the dogs were Cavalier King Charles spaniels (58 per cent).

The majority of the dogs had a combination of clinical signs present at the initial evaluation. Six dogs had all five of the clinical signs recorded (cough, collapse, exercise intolerance, exertion-induced dyspnoea and dyspnoea at rest) and a further nine dogs showed all the clinical signs except collapse.

Despite randomisation, a statistically significant difference in the mean mobility, demeanour and overall scores was present in the two treatment groups at baseline (Table 3). However, the difference in the

baseline dose of furosemide between the two groups was not significantly different ($P=0.33$) (Table 3). The remaining clinical and miscellaneous features of the two groups were similar at baseline (Table 3). The characteristics of the two groups at baseline were similar in terms of their ECG features, echocardiographic measurements and calculations, and laboratory data.

Outcome

Fifteen (68.2 per cent) of the dogs treated with pimobendan (P dogs) successfully completed the six-month trial period compared with nine (42.9 per cent) of the dogs treated with ramipril (R dogs) (Table 4). Four (18.2 per cent) of the P dogs versus 10 (47.6 per cent) of the R dogs had an adverse

HF outcome. Three (13.6 per cent) of the P dogs and two (9.5 per cent) of the R dogs were euthanased during the study period, for reasons unrelated to heart disease.

Outcome measures

There was four times the odds of an adverse HF outcome (in other words, dogs that were euthanased, died or discontinued the trial as a direct consequence of HF) in dogs treated with ramipril compared with pimobendan (OR 4.09, 95 per cent confidence interval [CI] 1.03 to 16.3, $P=0.046$) (Table 5). Factors identified that significantly predicted adverse HF outcome at the 5 per cent level included mobility score, overall score and total cough scores. None of the variables derived from blood pressure, ECG, echocardiography and

Table 4. Outcome

Feature	Pimobendan (%)	Ramipril (%)
Successfully completed	15 (68.2)	9 (42.9)
Died (HF)	0 (0.0)	4 (19.0)
Euthanased (HF)	4 (18.2)	4 (19.0)
Discontinued (HF)	0 (0.0)	2 (9.5)
Euthanased (other)	3 (13.6)	2 (9.5)
Adverse HF outcome	4 (18.2)	10 (47.6)

HF Heart failure

Table 5. Factors influencing adverse heart failure (HF) outcome

Factor (at baseline)	N	OR (95% CI)	P value	Conclusion – higher odds of adverse HF outcome for dogs
Mobility	41	3.64 (1.38-9.61)	0.009	With higher mobility scores
Overall score	43	1.36 (1.06-1.73)	0.014	With higher overall scores
Total cough score	43	1.62 (1.09-2.42)	0.017	With higher total cough scores
Study medication	43	4.09 (1.03-16.3)	0.046	Receiving ramipril

OR Odds ratio, CI Confidence interval

Table 6. Factors influencing maximum furosemide dose

Factor (at baseline)	N	Parameter estimate for model intercept	Parameter estimate for baseline furosemide dose	Parameter estimate for factor	P value	Conclusion – higher maximum furosemide dose for dogs
Exertion-induced dyspnoea*	43	-0.055	1.196	2.270	0.014	With exertion-induced dyspnoea
2D-Ao _d (d)/2D-LA _d (d) ratio	40	5.960	1.008	-8.312	0.040	With lower values of the ratio
Total cough score	43	0.086	1.169	0.485	0.041	With higher total cough scores
Respiratory rate (clinical examination)	33	-1.681	1.176	0.081	0.048	With higher respiratory rate
PCV	37	-6.111	1.221	16.0	0.050	With higher PCV

*Clinical sign present at initial evaluation, PCV Packed cell volume

Table 7. Factors influencing whether additional clinic visits for heart failure-related problems were necessary

Factor (at baseline)	N	OR (95% CI)	P value	Conclusion – higher odds of additional visits for dogs
Baseline furosemide dose	43	1.58 (1.07-2.35)	0.023	With higher baseline furosemide doses
Respiratory effort	43	4.36 (1.11-17.1)	0.035	With higher respiratory effort scores
Total T4	38	0.92 (0.85-1.00)	0.048	With lower total T4 values

laboratory data were associated with an adverse HF outcome.

Using maximum furosemide dose administered (mg/kg/day) as the dependent variable, and adjusting for baseline furosemide dose (this was a statistically significant predictor of maximum furosemide dose [P=0.001]), study medication was not a statistically significant factor in determining the maximum furosemide dose (P=0.64). However, the presence of exercise-induced dyspnoea at the initial evaluation and left atrial size were factors that influenced the maximum furosemide dose (Table 6).

Using the occurrence of one or more

additional clinic visits for the treatment of HF (yes/no) as the dependent variable, there was no statistically significant difference in the odds of additional clinic visits for the treatment of HF for dogs treated with ramipril compared with pimobendan (OR 2.89, 95 per cent CI 0.83 to 10.0, P=0.094). Baseline furosemide dose, respiratory effort score and serum total T4 concentration influenced this outcome measure (Table 7).

Endpoints

There did not appear to be a difference between the two treatment groups with regard to adverse events that did not lead

to withdrawal from the study, occurring over time (Table 8). There were similar proportions of dogs that had adverse events not leading to withdrawal from the study: 12 (57 per cent) dogs had adverse events in the ramipril group compared with 14 (64 per cent) dogs in the pimobendan group (chi-squared test P=0.90). However, some of these adverse events occurred prior to taking the study drug (at baseline). Excluding those that occurred at baseline, 50 per cent of the dogs had adverse events in the ramipril group compared with 64 per cent of the dogs in the pimobendan group (chi-squared test P=0.66).

Repeated measures analysis

The interaction between randomisation group and time was not statistically significant for any of the continuous data (quality of life questionnaire and clinical examination scores, blood pressure, ECG derived heart rate). This implies that the effect over time for each of the randomisation groups did not differ substantially. In other words, a

Table 8. Adverse events not leading to withdrawal from the study over time

Adverse event	Pimobendan		Ramipril	
	N	%	N	%
Vomiting	3	13.6	0	0.0
Diarrhoea	1	4.5	1	4.8
Sneezing	1	4.5	2	9.5
Pruritus	2	9.0	2	9.5
Skin rash	2	9.0	0	0.0
Confusion	1	4.5	3	14.3
Lameness	0	0.0	1	4.8
Collapse	0	0.0	3	14.3
Polydipsia	6	27.0	4	42.9
Ascites	1	4.5	0	0.0
Other	3	13.6	3	14.3

Table 9. Presence of ventricular premature complexes (VPCs) and supraventricular premature complexes (SPCs) over time in dogs treated with ramipril and pimobendan (intention-to-treat analysis)

	Number of dogs with factor present + number of dogs that were withdrawn or died (intention-to-treat %)							
	Baseline		One month		Three months		Six months	
	Pimobendan	Ramipril	Pimobendan	Ramipril	Pimobendan	Ramipril	Pimobendan	Ramipril
VPC	2+0 (9)	3+0 (14)	1+1 (9)	5+2 (33)	1+3 (18)	2+10 (57)	1+7 (36)	3+12 (71)
SPC	7+0 (32)	6+0 (29)	7+1 (36)	7+2 (43)	5+3 (36)	6+9 (71)	5+7 (54)	6+10 (76)

similar pattern occurred over time for both randomisation groups. Once the interaction was removed from the model, the treatment effect was then the weighted average effect over the time points. However, it was found that no statistically significant differences occurred between the two treatment groups for any of the continuous data considered.

Premature complexes

Table 9 gives the numbers of dogs where VPCs and SPCs were present and the number of dogs that had missing data for these measurements. An intention-to-treat analysis was conducted and it was assumed that those dogs with missing values of VPC and SPC had VPC and SPC present, respectively. The randomisation group and time interaction was not statistically significant. However, time was statistically significant for both VPC ($P < 0.001$) and SPC ($P = 0.003$). Additionally, there was a significantly higher ($P = 0.005$) proportion of R dogs with VPCs compared with P dogs, even after taking into account the effect of time. No significant difference between the proportion of R dogs and P dogs with SPCs ($P = 0.15$) was seen.

DISCUSSION

The present study was designed to evaluate the long-term efficacy and safety of pimobendan when administered orally at 0.3 mg/kg every 12 hours to dogs with naturally occurring HF caused by MMVD. Data were objectively compared in a single-blind fashion, allowing an unbiased comparison of the efficacy and safety of pimobendan with that of ramipril.

The findings demonstrated that dogs treated long term with pimobendan were 25 per cent as likely to have an adverse HF outcome compared with dogs treated with ramipril. However, although the difference in furosemide dose between the two treatment groups at baseline was without statistical significance (possibly a more reliable indicator of disease severity than an owner-completed quality of life questionnaire), a statistically significant difference was present in the mean mobility and demeanour scores for the two treatment groups at baseline. Since these were both significantly predictive of an adverse HF outcome, those dogs treated with ramipril may have had more advanced

disease at baseline than those treated with pimobendan.

Additionally, the CI was wide, ranging from an improvement in the pimobendan group that was not clinically important (lower bound CI 1.03) to a positive effect in the pimobendan group which was extremely large (upper bound CI 16). Therefore, a larger, more powerful study is required to determine whether or not drug treatment truly influenced the risk of adverse HF outcome in dogs in the present study.

An examination of baseline characteristics provides a useful insight into the natural history and other features of the disease. The enrolment of predominantly small-breed dogs, with a preponderance of Cavalier King Charles spaniels, supports previous observations regarding breed predisposition to MMVD (Darke 1995). Coughing was the most common clinical sign present prior to baseline, followed closely by exercise intolerance and exercise-induced dyspnoea.

It is often considered useful to determine whether or not the characteristics of the two treatment groups at baseline were

similar. In this particular case, there was a statistically significant difference in the mean mobility, demeanour and overall scores between the two treatment groups at baseline. However, as the study design included initial randomisation, performing an analysis adjusting for any factors that are not balanced subsequently is not recommended by the majority of statisticians (Kirkwood and Sterne 2003). The baseline differences between groups may represent a limitation of this study.

Few of the baseline characteristics influenced the occurrence of the three outcome measures. These findings are in accordance with those seen in humans with primary mitral regurgitation, in which the progression of mitral regurgitation is poorly predicted using baseline characteristics (Enriquez-Sarano and others 1999).

There were fewer adverse HF outcomes for P dogs compared with R dogs. This equated to P dogs being 25 per cent as likely to experience an adverse HF outcome compared with R dogs. However, the low statistical power of the study and the fact that dogs randomised to ramipril may have had more advanced disease, as previously discussed, means this finding should be interpreted with caution.

In contrast to concerns that positive inotropic agents acting through PDE III inhibition may increase mortality (Lynch and others 1988), the findings of the present study suggest that long-term treatment with pimobendan may have a significant protective effect. Although few of the baseline characteristics influenced the occurrence of adverse HF outcome, it is of interest that dogs with a higher mobility, overall cough score and/or total cough score at baseline were at increased odds for adverse HF outcome.

Higher scores for the clinical examination and quality of life questionnaire categories could reflect more advanced disease at baseline, and therefore may be associated with a poorer prognosis.

Maximum furosemide dose was used in the analysis as an outcome measure as this was considered to be a good indicator of

the severity of cardiac disease, provided that no other diuretics were administered concurrently. A statistically significant diuretic-sparing effect of either study drug compared with the other was not demonstrated. Although few baseline characteristics influenced the maximum furosemide dose, it is of interest that exertion-induced dyspnoea at the initial evaluation increased the maximum furosemide dose. Exertion-induced dyspnoea could reflect more advanced disease since, in most cases, signs of congestive failure precede those of forward failure (Kittleson and Kienle 1998b). It is also possible that dogs with lower two-dimensional (2D)-Ao_d (d)/2D-LA_d (d) ratios, higher total cough score and/or a higher respiratory rate at baseline had more advanced disease. A higher packed cell volume at baseline may reflect higher diuretic dose administration at this time, as this may produce a mild subclinical dehydrating effect.

Adverse events not leading to withdrawal from the study were common in both treatment groups. The difference in incidence of adverse events between the treatment groups was without statistical significance.

Much attention has been focused on a possible direct effect of pimobendan on the development of ventricular arrhythmias and elevation of heart rate. Concerns that positive inotropic agents acting through PDE III inhibition may exacerbate the development of ventricular arrhythmias (Lynch and others 1988) were not realised in the present study, since VPCs were recorded in a greater number of R dogs. Elevation of intracellular cAMP in cardiac tissues is known to cause an elevation of heart rate. However, the heart rate in the dogs remaining in the present study at each of the scheduled visits was similar for both treatment groups.

The significance of these findings should not be overstated since electrocardiography was only performed for a period of five minutes at each of the scheduled evaluations, and the data presented do not take into consideration those dogs that

withdrew from the study prematurely. A more thorough evaluation of heart rate and the prevalence of any arrhythmias would have required multiple 24-hour ECG analyses.

Interestingly, the results of the present study do not support the findings of previous studies in which male dogs with MMVD had a tendency towards a more rapid progression of the disease than females (Haggstrom and others 1992, Darke 1995, Kwart and others 2002). This can be inferred from the absence of influence of sex on the occurrence of the three outcome measures.

The number of cases was insufficient to permit detailed analyses of pimobendan and ramipril dosage subgroups. Notwithstanding local tissue enzyme inhibition, previous studies have demonstrated that the time required to return to 50 per cent of the difference between maximum and zero ACE activity (measured as an estimate of duration of activity) after the administration of ramipril (0.25 mg/kg) is significantly less than 24 hours (Hamlin and Nakayama 1998). It is therefore possible that more frequent ramipril administration may have been more efficacious.

Ramipril was chosen in the present study as a positive control to pimobendan since the addition of an ACE inhibitor to standard therapy has been demonstrated to be both efficacious and safe in dogs with HF caused by MMVD (COVE Study Group 1995, IMPROVE Study Group 1995, LIVE Study Group 1998, BENCH Study Group 1999). Notwithstanding the possible implications of differences in baseline characteristics between the randomisation groups, the results of the present study suggest pimobendan may be an acceptable alternative to ramipril in this setting.

Further studies of greater statistical power are required to identify whether pimobendan is equally effective or more effective than the ACE inhibitors. In spite of this, combined therapy with an ACE inhibitor and pimobendan may

be more efficacious than pimobendan alone, especially given that furosemide has been shown to stimulate renin secretion (Corsini and others 1975). The question of whether or not combined therapy has greater efficacy than either agent alone can only be answered with appropriate clinical trial data.

In order to evaluate quality of life objectively from the clinical examination and owner-completed questionnaire, specific categories were established and assigned a score. This was considered to be a more direct and comprehensive measure of the effects of therapeutic intervention than HF classification. Given the difference in adverse HF outcome, in contrast to what might have been expected, an improvement in quality of life in the dogs remaining in the study at each of the scheduled visits was not shown. The quality of life scoring system chosen for use in the present study has been reported previously and was used by the IMPROVE Study Group (1995).

However, there are possible limitations of such a scoring system. In a numerical system, the distance between each score may not be equal and, therefore, the scoring system cannot be regarded as linear. Furthermore, by adding the scores and the fact that some are scored from 0 to 3 and others from 1 to 5 means that a higher score for one parameter graded out of five carries more weight than a high score in a parameter graded out of three in the summation. This may be regarded as a limitation of a quality of life scoring system but, since both groups were scored in a similar way, the authors believe that comparison between the groups using this system was valid.

The primary outcome measure analysis was conducted on an intention-to-treat basis, and therefore all dogs contributed information. It was not possible to conduct the secondary outcome measure analyses on an intention-to-treat basis, since some data (from dogs that failed to complete the trial) were absent. However, in the secondary outcome measure analy-

ses, data obtained from dogs that failed to complete the trial were included up to the time at which they died, were euthanased or discontinued the trial. Therefore, dogs with only one follow-up visit were included and the majority of the dogs contributed information to the analyses.

Any analysis which does not take into consideration the missing data over time would be misleading. This was particularly the case in the present study because a much higher percentage of R dogs had missing data at six months due to greater incidence of adverse HF outcome compared with P dogs. If only data obtained at six months was compared, only data derived from dogs completing the trial would be included. This would not be representative of those dogs that started the trial or the intended study population. It is likely that those dogs which failed to complete the trial would have had a worse value for a particular variable compared with dogs that completed the trial successfully. The repeated measures analysis makes some allowance for the missing data as it is estimated from the covariance structure from the remaining observations. Therefore, the effects over time can be examined and the dogs that failed to complete the trial did not bias the results greatly.

The high incidence of adverse outcome initially seems surprising. However, an examination of the literature demonstrates that the results are in accordance with other veterinary clinical studies (IMPROVE Study Group 1995). Data cited by Kittleson and Kienle (1998a), from clinical trials of the use of milrinone, a pure PDE III inhibitor, in dogs with mild to moderate HF caused by valvular disease, show that 25 per cent of dogs died within the first six months. This figure increased to 50 per cent mortality at seven months in dogs with severe HF. The incidence of adverse outcome at six months in the present study was 47.6 per cent and 18.2 per cent in the ramipril and pimobendan treatment groups, respectively. This percentage includes dogs that withdrew

from the study due to worsening HF but which may have been alive at six months, and excludes those dogs that were euthanased for reasons unrelated to heart disease.

Several limitations of this study must be acknowledged. The major limitation was the relatively low number of cases, resulting in a relatively low statistical power, as indicated by the relatively wide CIs (1.03 to 16), showing odds of an adverse HF outcome. Obtaining a difference between two groups that is not statistically significant does not imply that there is no difference. It could be because there is no difference or because there is a lack of statistical power to detect a difference. Therefore, non-significant results should not be misinterpreted. Only relatively large differences will show up as statistically significant. So the fact that statistically significant differences have been found is important and these potentially important differences between the two treatment groups need to be examined further in a larger number of dogs.

Under the null hypothesis of there being no difference between groups, one would expect one in 20 of the statistical tests to be statistically significant at the 5 per cent testing level simply by chance. This is particularly important in the present study, in which a large number of factors have been analysed. However, because the present investigation was the first to have exclusively evaluated the long-term efficacy and safety of pimobendan in dogs with HF caused by MMVD, it was useful to examine a large number of variables as this could serve to highlight potentially important areas that might warrant further investigation.

Although the Doppler echocardiographic studies were carried out by three different echocardiographers at three locations, previous work investigating measurement repeatability between cardiologists with similar training and experience has shown that operator variability is not significant (Dukes-McEwan and others 2002). All operators in this study had

Doppler echocardiographic examinations peer-reviewed for inclusion on the Veterinary Cardiovascular Society-approved Doppler echocardiography list.

Conclusions

Treatment with pimobendan in dogs with mild to moderate HF caused by MMVD was well tolerated compared with treatment with ramipril. P dogs were 25 per cent as likely as R dogs to experience an adverse HF outcome. Further studies are necessary to determine whether these findings can be repeated in a larger number of dogs.

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