Acta Scientiae Veterinariae, 2014. 42: 1175.

RESEARCH ARTICLE
Pub. 1175

ISSN 1679-9216

Pimobendan Improves Clinical Signs in Short Term Compared to Digoxin or Placebo in Dogs with Heart Failure Due to Chronic Degenerative Mitral Valve Disease

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ABSTRACT

***Background*:** Chronic degenerative mitral valve disease (CDMVD) continues to be the most common cause of heart failure (HF) in small breed dogs. Pimobendan (PIMO) is a mixed action drug with inotropic and vasodilator properties and is widely used to treat heart disease in dogs. Therefore, PIMO increases cardiac output, reduces both preload and afterload and increases myocardial contractility without increasing energy consumption and myocardial oxygen. Digoxin (DIG) is a cardiac glycoside acting through inhibition of the sarcolemmal Na+/K+ ATPase pump, hence increasing intracellular calcium. It exerts beneficial effects on left ventricular function, symptoms and exercise tolerance. The purpose of this prospective, randomized, double blind clinical trial was to evaluate the clinical response and QoLQ in heart failure (HF) dogs treated with digoxin or pimobendan in addition to conventional therapy (furosemide and benazepril).

***Materials, Methods & Results*:** Inclusion criteria: dogs in class III or stabilized class IV (NYHA). Exclusion criteria: use of positive inotrope and antiarrhythmic, presence of atrial fibrillation, renal or hepatic disease or neoplasia. Thirty three dogs were included and randomly assigned to DIG (n = 11), PIMO (n = 14) and placebo (PL) (n = 8) and followed up weekly. Data was evaluated for days zero, 7, 14 and 28. Increasing score was assigned to each variable depending on worsening of clinical evaluation (history and physical exam, QoLQ and echocardiogram (echo).Three dogs died during treatment due to worsening of HF, one of PL group and two of DIG group; furthermore, one of PIMO group was censored due to worsening of heart failure. There was no significant difference between and within groups for echo and radiography. PL and DIG groups did not show any significant difference throughout the 28 days of treatment. PIMO group showed lower physical exam score and increased early mitral inflow velocity on day 28. Serum creatinine increased on days 14 and 28 compared to baseline, but within normal limits. The groups were similar within each evaluation day.

***Discussion*:** This is the first short term prospective randomized double blind study comparing PIMO to DIG or PL additionally to conventional therapy (ACEi and furosemide) for dogs with HF due to CDMVD. It was observed an early significant clinical improvement in dogs receiving PIMO compared to those receiving DIG or PL. The increase in early mitral inflow velocity (E-wave) on day 28 for PIMO group is suggestive of diastolic dysfunction improvement, but this is only one variable related to diastolic function. Creatinine concentration increased in PIMO group, although it remained within normal range. In the present study, although all the three groups received furosemide, only PIMO group showed increase in blood creatinine between baseline and days 7 and 28. This result must be explored in later studies. Regarding the exercise intolerance assessment in a QoLQ, it must be aware that the owner evaluation is strongly influenced by the level of exercise that the dog is regularly submitted. Considering that most of the times, small breed dogs in a more advanced age is probably more sedentary and this fact surely precludes the owner to assess the exercise capacity. A more objective evaluation of the exercise tolerance should be considered in further clinical trials. Probably because of the small number of animals included in this study, differences in other studied variables were not found. The short-term follow-up of these patients may also have influenced the lack of differences among groups. Considering that stronger clinical evidence is needed to guide clinical decisions, longer prospective studies are also needed to compare the effects of DIG and PIMO, as well as to consider the benefits of the use or not of DIG associated with PIMO for dogs in HF due to CDMVD.

Keywords: treatment, inotropic drug, angiotensin converting enzyme inhibitor, furosemide.

Received: 15 September 2013 Accepted: 28 January 2014 Published: 4 February 2014

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INTRODUCTION

Pimobendan (PIMO) is a mixed action drug with inotropic and vasodilator properties and is widely used to treat heart disease in dogs [3,7]. It is a benzidazole-pyridazinone derived that exerts effect by combining inotropic and vasodilator calcium sensitization to troponin C and inhibition of phosphodiesterase [3,17]. Therefore, PIMO increases cardiac output, reduces both preload and afterload and increases myocardial contractility without increasing energy consumption and myocardial oxygen [11]. Its use has shown good results in dogs with myxomatous mitral valve [11,12] and in dogs with dilated cardiomyopathy [14]. Digoxin (DIG) is a cardiac glycoside acting through inhibition of the sarcolemmal Na+/K+ ATPase pump, hence increasing intracellular calcium. It exerts beneficial effects on left ventricular function, symptoms and exercise tolerance [13]. Some clinical studies have shown that PIMO leads to clinical improvement as well as of quality of life (QoLQ), but mostly, the comparison was made with placebo or benazepril, and not with another positive inotrope. Thus, the aim of this study was the clinical evaluation and quality of life questionnaire (QoLQ) as well as systolic arterial blood pressure (SAP), electrocardiography (ECG), echocardiography (ECHO), thoracic radiography, hematological and biochemical parameters in dogs with HF caused by CDMVD (associated or not with tricuspid insufficiency without right ventricular failure signs), submitted to conventional therapy (ACEi, furosemide), with and without DIG compared to conventional therapy associated to PIMO.

MATERIALS AND METHODS

This study was performed between November 2009 and November 2011 at the Veterinary Medical Teaching Hospital, School of Veterinary Medicine and Animal Science, University of São Paulo and at PROVET Laboratory of Hormone Testing. The owners of the dogs used in this study were informed about the research study proceedings, who signed a consent and commitment form.

A prospective, randomized, double-blinded, placebo-controlled study was conducted. Small breed dogs (up to 15 kg), independent of gender, age and breed definition, with HF clinical signs were assessed by anamnesis, physical exam (PE), ECG[1], thoracic radiography[2], ECHO[3], systolic arterial blood pressure (SAP)[4] hematological and biochemical profile, as well as electrolytes determination[5] and thyroid function evaluation (free T4 and canine TSH)[6].

Patients were classified according to New York Heart Association (NYHA) [10], based on clinical exam. Only those in class III (having shown at least one episode of HF decompensation) were included in the study. Any patients showing signs of infection, endocrine diseases, hepatic changes or renal disease were excluded.

Information regarding anamnesis and physical exam were assigned a score to allow a more objective assessment.

For anamnesis, the information considered was: cough (0=absent, 1=mild to moderate and 2=severe), lethargy/willingness to exercise (0=absent, 1=mild to moderate and 2=severe), exercise intolerance (0=absent, 1=mild to moderate and 2=severe), and dyspnea (0=absent, 1=mild to moderate and 2=severe). The presence of seizure, syncope, presyncope, cyanosis, ascites and limbs edema were also considered (0=absent and 1=present). Anamnesis score varied from zero to 14.

Physical exam (PE) parameters were: general appearance (0=good, 1=regular and 2=compromised/bad); respiratory pattern (0=eupneic, 1=tachypneic and 2=dyspneic); hydration status (0=adequate/normal and 1=dehydrated); mucous membranes (0=normal, 1=pale and 2=cyanotic), capillary refill time (CRT) (0=normal and 1=prolonged); femoral pulse (0=normokinetic, 1=hyperkinetic and 2=hypokinetic); cardiac rhythm (0=regular and 1=irregular); cardiac sounds (0=normophonesis, 1=hyperphonesis and 2=hypophonesis); cardiac murmur grade varying from 1 to 6 based on Friedman's scale) and, pulmonar auscultation (0=no alteration, 1=focal crackles and 2=generalized crackles). PE score varied from zero to 27.

A QoLQ questionnaire was also used [11]. QoLQ assessed: exercise tolerance (0=very good, 1= good, 2=moderate, 3=bad and 4=very bad); cough (0=absent, 1=occasional, 2=frequent and 3=persistent); respiratory effort (0=normal, 1=mildly increased, 2=hard to breath and 3="shortness of breath"; appetite, (0=increased, 1=normal, 2=decreased and 3=anorexia); mental status (0=alert and responsive, 1=mildly decreased, 2=depressed and 3=little responsive); attitude (0=increased, 1=unaltered and 2=decreased; physical activity (0=good, 1=moderate, 2=decreased, 3=minimal and 4=incapacitated. QoLQ score varied from zero to 22.

ECG was evaluated based on Tilley [21]. Thoracic radiography was evaluated by Vertebral Heart Size (VHS) according to Buchanan and Bücheler [6], as well as for presence of congestion/edema. SAP was performed by non invasive technique, by Doppler method, as proposed by Brown *et al*. [5] and Ware [22].

Echocardiographic examinations were performed according to the American Society of Echocardiography (ASE) recommendations [2]. The M-mode parameters evaluated were as follows: thickness of the interventricular septum in diastole (IVSd); thickness of the left ventricular free wall in diastole (LVWd); ratio between IVSd and LVWd (septum/wall ratio); internal diameter of the left ventricular cavity in diastole (LVDd); internal diameter of the cavity of the left ventricle in systole (LVDs); left ventricular ejection fraction (LVEF); fractional shortening (FS); heart rate (HR); aortic root (Ao); left atrium (LA); ratio between the aortic root and left atrium measurements (Ao/LA). Three measurements were performed for each echocardiographic parameter, and the mean of the three values was considered for analysis.

Hematological and biochemical profile (liver enzymes, renal function and electrolytes), free T_4 (dialysis) and canine TSH were also performed.

This was a double-blinded study and only two collaborators were responsible for dispensing of drugs. Randomization was performed by drawing lots and just these collaborators knew which medication was used.

Dogs were followed up for four weeks (28 days). Clinical evaluation (anamnesis, PE and QoLQ), ECG, ECHO, SAP, laboratory evaluation were performed on baseline (day zero), and then on days 7, 14 and 28 of therapy. Thoracic radiography was performed on baseline and day 28, and thyroid test (T_4 and TSH) only on baseline.

The medications and doses used according to the group assignment were: ACEi (benazepril)[7] 0.5 mg/kg SID, PO; furosemide[8] 2.0 mg/kg BID or TID, PO; DIG[9] 0.003 to 0.008 mg/kg BID, PO; PIMO[10] 0.2 mg/kg BID, PO, 1 h before meal. PIMO was remanipulated[11] with Vetmedin®, sorbitol and potassium sorbate. PL containing sorbitol and potassium sorbate was manipulated[11]. All drugs evaluated (DIG, PIMO and PL) were compounded in liquid presentation from original commercial available formulations in order to ensure treatment blindness.

When death or need for further treatment intervention that forced label opening occurred, scores were considered as maximum for the following evaluations, as an intention to treat design.

Shapiro-Wilk test was used to assess normality of distribution. Within group analysis was performed by Repeated measures ANOVA followed by Tukey--Kramer as post hoc test (for parametric data) and Friedman's test followed by Dunn for nonparametric data. For comparison between groups, ANOVA was used followed by Tukey as post hoc test for parametric data and Kruskal-Wallis followed by Dunn for nonparametric data. Significance was considered when $P < 0.05$. Statistical analysis was performed using commercial available software (GraphPad InStat 3 version 3.05, GraphPad Software, San Diego, California, USA).

RESULTS

Forty nine animals were screened, but 16 were excluded with different diagnosis or incident comorbidities: pancreatitis (1), absence of edema and congestion (2), urolithiasis (1), abdominal neoplasia (2), death from heart failure before ECHO exam (3), liver disorders (1), breast cancer (1), epilepsy (1), atrioventricular block (1), dog owner was sick (1) and because ECHO machine broke during study (2).

Thirty three dogs were included in the study, and were randomly allocated to three groups: group PL: 8 dogs treated with ACEi (benazepril), furosemide and PL; group DIG: 11 dogs treated with ACEi (benazepril), furosemide and DIG; group PIMO: 14 dogs treated with ACEi (benazepril), furosemide and PIMO (Table 1).

For the comparison between groups, within each moment (Day 0 vs Day 7 vs Day 14 vs Day 28), the groups were similar for all the variables studied. At day 28, there was a significant difference among groups for physical exam score ($P = 0.02$), but it was not possible to identify the difference after the post hoc test.

For comparison among moments within each group, PL and DIG groups did not show any significant difference throughout the 28 days of treatment. For PIMO group, anamnesis score decreased on day 14 compared to baseline, but the difference did not reach significance at day 28. PIMO group showed lower physical exam score on day 28 ($P < 0.05$). Quality of life questionnaire score was significantly lower on day 7, but this difference did not reach significance on days 14 and 28.

There was an increase in early mitral inflow velocity (E-wave) on day 28 for PIMO group. There was a significant difference among groups for urea concentration, but the difference was not apparent after pos hoc test. Creatinine concentration increased on days 14 and 28 compared to baseline for PIMO group, although remaining within reference range for 13 out of 14 dogs, with slight increase in one dog (Table 2).

Table 1. Characteristics of groups regarding sample size, number of deaths and censored, age, weight, gender and breed of included patients.

Parameter	Groups Descriptions			
	PL group (n=8)	DIG group (n=11)	PIMO group (n=14)	ALL groups (n=33)
Died	1 (12.5%)	2 (18.2%)	0	3 (9.1%)
Censored	0	0	1 (7.1%)	1 (3%)
Age (years)	12 (8-14)	10.8 (8-14)	11.9 (9-15)	11,6 (8-15)
Median (min-max)				
Weigh (kg)	6.6 (1.9-11.3)	6.8 (4.2-13.1)	6.1 (1.7-12.6)	6.5 (1.7-13.1)
Median (min-max)				
Gender	4 M(50%)	7 M (63.6%)	10 M (71.4%)	21 M (63.6%)
	4 F (50%)	4 F (36.4%)	4 F (28.6%)	12 F (36.4%)
Breed	2 Poodle (25%)	6 Poodle (54.5%)	8 Poodle (57.1%)	16 Poodle (48.5%)
	1 Pinscher (12.5%)	1 Teckel (9.1%)	2 Pinscher (14.3%)	3 Pinscher (9.1%)
	2 Teckel (25%)	1 Shih tzu (9.1%)	1 Yorkshire (7.1%)	3 Teckel (9.1%)
	3 MB (37.5%)	1 Schn. (9.1%)	3 MB (21.4%)	1 Shih tzu (3%)
		2 MB (18.2%)		1 Yorkshire (3%)
				1 Schnauzer (3%)
				8 MB (24.2%)

M: male; F: female; Schn: Schnauzer; MB: mixed breed.

DISCUSSION

This is the first short term prospective randomized double blind study comparing PIMO to DIG or PL additionally to conventional therapy (ACEi and furosemide) for dogs with HF due to CDMVD. We observed an early significant clinical improvement in dogs receiving PIMO compared to those receiving DIG or PL.

A Pubmed search using "Pimobendan" AND "Heart failure" AND "dogs" as search strategy recovered 28 articles, including six clinical trials. A modified search with "Pimobendan" AND "dogs" recovered 80 publications, 11 of which were clinical trials. Among these, one was focused on pulmonary hypertension and three were related to HF due to CDMVD comparing pimobendan (PIMO) and an angiotensin converting enzyme inhibitor (ACEi). These studies have shown that PIMO improves survival and heart insufficiency score. Although digoxin (DIG) is not a strong positive inotrope, it has been used for the management of heart failure in dogs with CDMVD when there is left ventricular dilation or myocardial dysfunction. ACEis have been proved to have beneficial effects on survival and quality of life in dogs with HF due to CDMVD, and therefore, are widely used with this purpose. Most of the studies, cited herein, evaluated PIMO compared to an ACEi; however, there is a lack of studies assessing the additional effects of PIMO on a standard therapy, which already includes ACEi and diuretics, nor has anyone compared PIMO to DIG besides a placebo (no positive inotrope).

On a study comparing PIMO and ramipril in dogs with CDMVD, the authors reported that dogs in the ramipril group had a higher overall score on baseline, and therefore, they may have had more advanced disease than the dogs treated with PIMO [19]. In the present study, all the groups were comparable (similar) on baseline.

Table 2. Summary of statistics for anamnesis, physical exam, quality of life questionnaire scores, urea, creatinine and mitral inflow velocities measured by Echo-Doppler. HOVET/FMVZ/USP. São Paulo, 2009-2011.

Within Groups Analysis								
Variable	Day	PL group	*p* value	DIG group	*p* value	PIMO group	*p* value	Post Hoc Test
								PIMO Group
Anam. Score	0	3.63±2.72	0.11[#]	3.82±2.36	0.17[#]	2.86±2.25	0.002[#*]	T0>T14[£]
	7	1.63±1.85		1.73±1.49		0.93±1.07		
	14	1.63±1.41		3.36±5.39		0.86±1.10		
	28	2.63±4.75		3.18±5.40		1.57±3.67		
PE Score	0	7.00±2.88	0.57[#]	7.82±3.63	0.88[#]	6.14±1.79	0.006[#*]	T0>T28[£]
	7	5.75±1.75		6.18±1.78		5.00±1.41		
	14	6.25±1.91		9.55±8.77		4.64±1.95		
	28	8.50±7.62		9.36±8.79		5.86±6.35		
QoLQ Score	0	8.00±3.63	0.08[#]	6.18±2.48	0.10[#]	7.57±3.80	0.01[#*]	T0>T7[£]
	7	4.63±3.42		4.82±2.86		3.86±2.07		
	14	6.63±3.74		8.00±7.31		4.64±3.1		
	28	5.63±6.74		6.18±7.88		4.71±5.24		
Ureia	0	78.06±22.32	0.69[#]	77.32±47.76[&]	0.25[#]	55.05±22.94[&]	0.04[#*]	NS[£]
	7	89.89±61.58		91.82±68.20[&]		70.92±20.23		
	14	87.96±46.03		94.59±59.42[&]		72.53±25.08		
	28	107.59±80.27[&]		92,91±49.03		74.03±33.44[&]		
Creatinin	0	1.13±0.45[&]	0.24[#]	1.10±0.38	0.40[#]	0.85±0.30[&]	0.02[§*]	T0<T14 and T28[¢]
	7	1.22±0.64[&]		1.29±0.44		1.06±0.26		
	14	1.34±0.70[&]		1.31±0.39		1.03±0.31		
	28	1.35±0.76[&]		1.37±0.52[&]		1.06±0.36		
E	0	1.29±0.32	0.84[§]	1.20±0.31	0.99[§]	1.38±0.24	0.03[§*]	T0>T28[¢]
	7	1,24±0.25		1.19±0.32		1.31±0.24		
	14	1.31±0.39[&]		1.12±0.32		1.28±0.25		
	28	1.36±0.33		1.13±0.30		1.23±0.17		
A	0	0.69±0.12	0,484[§]	0.82±0.24	0,24[§]	0.70±0.17	0,567[§]	NS
	7	0.76±0.19		0.84±0.24		0.68±0.18		
	14	0.80±0.25		0.70±0.17		0.70±0.14		
	28	0.77±0.17		0.75±0.15		0.66±0.14		
E/A	0	1.92±0.65	0.62[§]	1.55±0.51[&]	0.18[#]	2.11±0.61	0.68[§]	NS
	7	1.74±0.53		1.45±0.32		2.05±0.58		
	14	1.84±0.87		1.61±0.31		1.90±0.53		
	28	1.88±0.72		1.56±0.43		1.93±0.47		

Anam.: anamnesis; PE: physical exam; QoLQ: quality of life questionnaire; Cr: creatinine; E: early mitral inflow velocity; A: late mitral inflow velocity; NS: no statistical difference; [#]Kruskal-Wallis rank sum test; [§]ANOVA for repeated measures; [£]Dunn's Multiple Comparisons Test; [¢]Tukey-Kramer Multiple Comparisons Test; [&]Shapiro-Wilk - Abnormal distribution; *Statistical difference.

In a study published as an abstract that included 15 dogs with CHF secondary to CDMVD receiving furosemide and benazepril or PIMO, the authors subjectively observed a 100% improvement on PIMO group and only 20% on the benazepril group [15].

Previous longer term studies also comparing PIMO and benazepril, observed a longer survival time for PIMO group with median survival of 415 compared to 128 days, respectively [12], and 267 days versus 140 days, respectively [10]. The number of dogs included in the present study and the time of follow-up did not allow for survival analysis.

Dogs with asymptomatic DCMVD presented increase of left ventricular ejection fraction after 30 days therapy with PIMO [16], differently from what was observed in our study in a 28 days follow-up.

The increase in early mitral inflow velocity (E-wave) on day 28 for PIMO group is suggestive of diastolic dysfunction improvement, but this is only one variable related to diastolic function. Accelerated LV isovolumetric relaxation and improved distensibility was observed in an experimental study on pacing induced HF in dogs treated with PIMO [1].

Creatinine concentration increased in PIMO group, although it remained within normal range. This finding is surprising because, another experimental study [11], with Beagles with induced CDMVD, observed increase of both renal blood flow and glomerular filtration rate in the second and fourth weeks using PIMO.

Alterations of renal function were not observed in healthy animals, receiving PIMO for seven days [9] and neither in a study of acute effects of PIMO and furosemide on renin-angiotensin-aldosterone system [18]. On the other hand, on a clinical study comparing effects of PIMO and benazepril, in Cavalier King Charles Spaniel dogs with CDMVD, despite the clinical improvement observed when low doses of furosemide were administered, there was an increase of blood creatinine levels [10]. In the present study, although all the three groups received furosemide, only PIMO group showed increase in blood creatinine between baseline and days 7 and 28. This result must be explored in later studies.

Regarding the exercise intolerance assessment in a QoLQ, we must be aware that the owner evaluation is strongly influenced by the level of exercise that the dog is regularly submitted. We must consider that most of the times, small breed dogs in a more advanced age is probably more sedentary and this fact surely precludes the owner to assess the exercise capacity. A more objective evaluation of the exercise tolerance should be considered in further clinical trials.

Probably because of the small number of animals included in this study, differences in other studied variables were not found. The short-term follow-up of these patients may also have influenced the lack of differences among groups. In agreement with other study [17], further clinical trials are needed to better assess the efficacy and safety of PIMO in dogs with CDMVD. Considering that stronger clinical evidence is needed to guide clinical decisions, longer prospective studies are also needed to compare the effects of DIG and PIMO, as well as to consider the benefits of the use or not of DIG associated with PIMO for dogs in HF due to CDMVD.

CONCLUSION

This short-term study suggests that dogs with CHF caused by CDMVD submitted to conventional therapy (ACEi and furosemide) associated with PIMO show early clinical improvement when compared to those receiving PLA or DIG.

SOURCES AND MANUFACTURERS

[1]ECAFIX ECG 6, Transform, São Paulo, SP, Brazil.

[2]Radiographic system (FUJI), Fujifilm Medical Corporation, Honshu, Tokyo, Japan.

[3]Vivid 7, GE Vingmed Ultrasound AS, Horten Vestfolf, Norway.

[4]Doppler Vascular DV610B, Medmega, Franca, SP, Brazil.

[5]Clinical Laboratory (Laboratório Clínico), FMVZ, USP, São Paulo, SP, Brazil.

[6]PROVET Laboratório de Dosagens Hormonais - I.D.E.), São Paulo, SP, Brazil.

[7]Fortekor®, Novartis Santé Animale S.A.S., Huningue, Alsace, France.

[8]Lasix®, Sanofi Aventis Farmacêutica Ltda, Suzano, SP, Brazil.

[9]Digoxina elixir®, Glaxosmithkline, Rio de Janeiro, RJ, Brazil.

[10]Vetmedin®, Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO, USA.

[11]Fórmula Médica Manipulation Pharmacy, São Paulo, SP, Brazil.

***Funding*.** This project was financially supported by FAPESP - São Paulo Research Foundation, process number 08/57620-2.

***Ethical Approval*.** The study was approved by the Ethics Committee on animal use at FMVZ-USP (process number 2008/1492).

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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