



Effects of Short-term Treatment with Pimobendan in Dogs with Myxomatous Valve Disease

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Abstract

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The aim of the study was to evaluate the short-term effects of pimobendan, a novel drug, in dogs with naturally occurring mitral valve myxomatous disease. The study involved twenty dogs with no previous treatment. The results show that pimobendan is well tolerated and can be administered effectively and safely in the treatment of congestive heart failure myxomatous mitral valve disease of the dog.

Keywords: Pimobendan, CHD, myxomatous mitral valve, heart, dog.

Introduction

The classical treatment for the control of signs due to congestive heart failure (CHF) includes diuretics, vasodilators and antiarrhythmic drugs. Pimobendan (Vetmedin®) is a novel drug with phosphodiesterase-inhibiting and calcium-sensitising effects that increase myocardial contractility, promote arterial and venous dilatation and could be effective for the treatment of congestive heart failure (CHF) in dogs. (Smith *et al.*, 2005; Gordon *et al.*, 2006; Lombard *et al.*, 2006; Kanno *et al.*, 2007; Häggström *et al.*, 2008). The aim of the study was to evaluate the short-term effects of

pimobendan on clinical, laboratory, radiological, electrocardiographic and echocardiographic observations in dogs with naturally occurring mitral valve myxomatous disease.

Materials and Methods

The present study was a prospective, descriptive, observational study (before and after trial). We considered just one working group: Dogs suffering from Congestive Heart Failure (CHF) due to myxomatous valve disease (MVD). The criteria included were: dogs present with a moderate to high intensity heart murmur with maximal intensity over the mitral area, with echocardiographic evidence of mixomatous mitral valve disease, evidence of moderate to severe left atrial or left

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ventricular enlargement on B-dimensional study and mitral regurgitation in colour Doppler study. The dogs did not show any evidence of other significant systemic disease or CHF due to congenital heart disease.

The study involved twenty patients with CHF secondary to MVD in phases 2 or 3 according to the Scandinavian modified New York Heart Association system (Kvart *et al.*, 2002), with no previous treatment. Patients were attended in the Cardiology Service of the Faculty of Veterinary Medicine at the Complutense University, Madrid. Clinical history, complete physical examination including body weight and electrocardiographic study were made. Radiological study, including right lateral and dorso-ventral thoracic radiograph, to determine the degree of

cardiomegaly according to the cardio-vertebral index and the degree of congestion-oedema in the lung was made. Finally, an echocardiographic study and a routine

Table 1
Dose schedule

Body weight (kg)	Pimobendan dosage		
	Daily dosage (mg)	First dose (morning)	Second dose (evening)
6.25-12.5	≈ 2.5	1x1.25 mg	1x1.25 mg
12.6-21	≈ 5	1x2.5 mg	1x2.5 mg
21.1-29	≈ 7.5	1x5 mg	1x2.5 mg
29.1-37	≈ 10	1x5 mg	1x5 mg

The statistical study was carried out with STATGRAPHICS Plus 5.0 (Statistical Graphics®).

Table 2a
Classification of the severity of clinical symptoms in study patients.

	Appetite	Demeanour	Exercise tolerance ^a	Respiratory effort	Cough	Nocturnal dyspnoea/coughing ^b	Heart insufficiency score (NYHA) ^c
0	Increased	Alert	Very good	Normal	None	None	1
1	Normal	Mildly depressed	Good	Mildly increased rate on effort	Occasional (a few times a week)	Slight symptoms	2
2	Decreased (about 2/3 of normal)	Moderately depressed	Moderate	Moderately laboured	Frequent (a few times each day)	Obvious symptoms	3
3	Markedly decreased (< 2/3 of normal)	Minimally responsive	Poor	Severe respiratory distress	Persistent (frequently during the day)	No information	4
4	Unresponsive						

^a**Very good:** Dog moves around with ease, capable of climbing stairs, alert and responsive to external stimuli, dog is able to do all exercise. **Good:** Dog moves around with ease, capable of climbing stairs, alert and responsive to external stimuli, dog is not able to do full exercise, ability of running is reduced. **Moderate:** Dog is less active than normal, moves around a few times per day, has difficulties with stairs, and avoids long walks. **Poor:** Dog is inactive, only gets up to eat, drinks or urinates, and is unable to climb stairs.

^b**Slight symptoms:** Dog is coughing from time to time during the night, but no other clinical signs of dyspnoea or uneasiness are present. **Obvious symptoms:** Dog shows symptoms of coughing, increased respiratory effort or uneasiness during the night.

^c**Score 1:** Asymptomatic dog with murmurs but no cardiac enlargement. **Score 2:** Asymptomatic dog with murmurs cardiac enlargement but no pulmonary oedema or congestion. **Score 3:** moderately symptomatic dog (dyspnoea, increased heart rate and disappearance of sinus arrhythmia) with murmurs, cardiac enlargement and interstitial pulmonary oedema. **Score 4:** Severely symptomatic dog with murmurs, cardiac enlargement and pulmonary oedema.

haematology and clinical chemistry were also performed. The data was collected on unseated patients using the usual cardiologic standards on an outpatient basis. The echocardiographic examination was performed to compare the effects of the drug on heart chamber size and wall motion. The echocardiographic measurements included fractional shortening, left ventricular internal dimensions in systole and diastole, internal dimension of left atrium and dimension of aorta.

All the animals included in the study were fed during the study period with a commercial or home hyposodic diet. All the patients were reviewed weekly and a record was kept of possible secondary effects or intolerance to treatment, especially cough and/or cardiac arrhythmias. Four weeks after the beginning of treatment, the initial tests were repeated in order to compare the final state of patients with the initial data. The symptoms described in the anamnesis of this first visit were classified according to severity and are shown in Tables 2 a, b.

Medical treatment involved the administration of pimobendan (Vetmedin®)

according to the dosing schedule instructions of the manufacturer (Boehringer Ingelheim Vetmedica GmbH, Germany).

Results and Discussion

In general, most patients improved with regard to clinical symptoms (Table 2). Intolerance to exercise showed a clear and significant improvement throughout the study, with the result that all patients had a lower degree of intolerance after treatment.

The radiological study showed that the degree of pulmonary congestion decreased significantly (Fig. 2a,b). Echocardiographic study showed a significant increase in the fractional shortening value.

At the moment, the therapy of cardiac insufficiency is based on two principles: reduction of the heart work and strengthening of its contractility, pimobendan showed both properties. We observed a good outcome in the patients during the period of study (Table 3) similar to other clinical trials (Gordon *et al.*, 2006; Lombard *et al.*, 2006; Kanno *et al.*, 2007; Häggström *et al.*, 2008; Oullet *et al.*, 2009)

Table 2b
Classification of the severity of clinical symptoms in study patients (continued)

	Electro- cardiography	Radiographic cardiomegaly	Radiographic pulmonary oedema	Clinical efficacy (at the end of study) ^d	Tolerance ^e
0	No abnormal findings	None	None	Very good	No adverse effects
1	Arrhythmia	Slightly enlargement	Mildly increased density	Good	Adverse event
2	Atrial fibrillation	Moderately enlargement	Moderately increased density	Sufficient	
3	Other ECG findings	Severe enlargement	Alveolar pattern	Insufficient	
4			Severe consolidation	Treatment failure	

^d**Very good:** Strong improvement in clinical condition. **Good:** Improvement in clinical condition. **Sufficient:** Slight improvement in clinical condition. **Insufficient:** No improvement in clinical condition. **Treatment failure:** such cases with persistent dyspnoea, progressive ascites, severe cardiac cachexia, severe exercise intolerance despite receiving diuretic drugs.

^eAdverse event: include vomiting, tachycardia, uneasiness, and others.

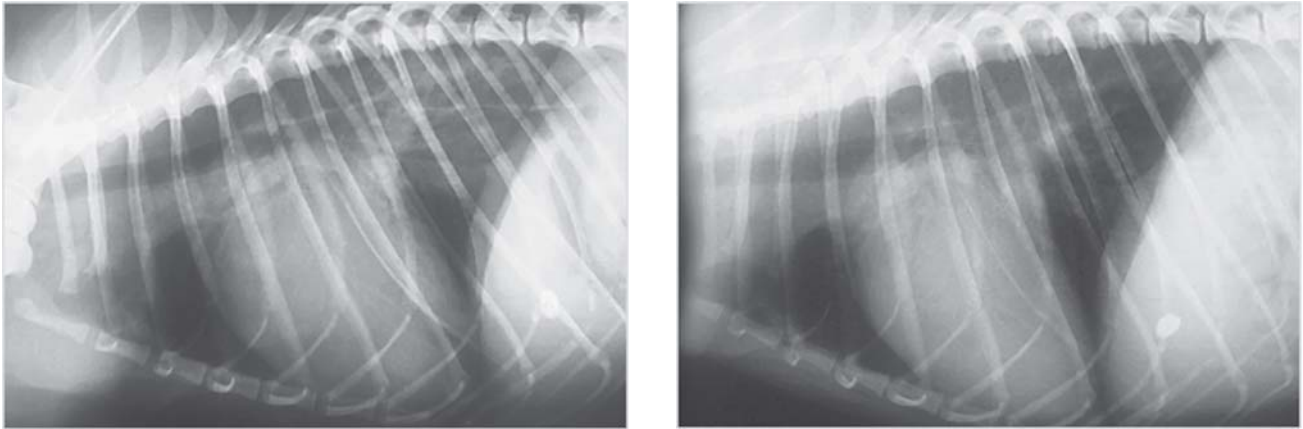


Fig. 1. Right lateral radiographic of a patient before (a) and after (b) treatment with pimobendan. Observe oedema in the perihilar zone and dorsal aspect of the lungs in the first figure but none after treatment

Table 3
Clinical, echocardiographic, haematological and biochemical findings

	Before treatment n=20	After treatment n=20
Appetite*	1.65±0.67	1±0.5
Demeanour*	1.5±0.6	0.47±0.5
Exercise tolerance*	1.65±0.74	1.1±0.6
Respiratory effort*	1.4±0.68	0.63±0.59
Cough*	1.55±0.68	0.57±0.6
Nocturnal dyspnoea*	1.2±0.52	0.63±0.5
CHF score*	2.75±0.5	2.1±0.56
Cardiomegaly	1.95±0.8	1.78±0.8
Pulmonary oedema*	1.7±1.03	0.73±0.73
Heart rate (bpm)	154±22.8	151.7±22.7
Arrhythmia	2	2
Fractional shortening (%)*	34.8±12	40.5±12
LVID systole	22.5±13	20.7±13
LVID diastole	38.5±13	37.9±14
Hct (%)	44.4±4.6	43.8±4.6
Glucose (mg/dl)	96.9±9.9	96.8±11
Urea (mg/dl)	35.3±11.8	33±14.5
Creatinine (mg/dl) *	1.08±0.2	0.97±0.15
ALT (U/L) *	46.5±54	27±12

*highly significant difference between the two groups.

There is evidence that pimobendan in addition to standard therapy, will increase survival in dogs with CHF secondary to MVD. (Gordon *et al.*, 2006; Lombard *et al.*, 2006, Häggström *et al.*, 2008). There was no mortality in this study either. With respect to security, the patients in this study did not develop arrhythmias and the heart frequency was stable during the study. We did not observe adverse changes in biochemical parameters especially with respect to renal and hepatic function. These results agree with other clinical trials (Gordon *et al.*, 2006; Lombard *et al.*, 2006). We did not find any undesirable outcomes in the patient but this might be due to the short period of study. Longer period studies are warranted to prove it.

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