A review of the pharmacology and clinical uses of pimobendan

Kimberly L. Boyle, DVM and Elizabeth Leech, DVM, DACVECC

Abstract

Objective – To review the pharmacology, research developments, and clinical uses of pimobendan
Data Sources – Original research articles and clinical studies from 1984 to August 2011.
Veterinary Data Synthesis – Pimobendan is approved for use in dogs for the treatment of congestive heart failure (CHF) secondary to chronic valvular heart disease (CVHD) and dilated cardiomyopathy (DCM). Expert-based veterinary guidelines recommend the use of pimobendan in the management of acute, hospital-based therapy for patients with CHF attributable to CVHD.
Conclusions – The use of pimobendan, an inodilator with phosphodiesterase 3 (PDE3) inhibitory and calcium-sensitizing properties, is regarded as a component of the standard of care in the management of dogs with CHF secondary to both DCM and CVHD. Further studies are warranted to confirm the safety and efficacy of pimobendan for the off-label use of this drug in asymptomatic CVHD, pulmonary arterial hypertension, asymptomatic myocardial diseases, CHF from all other causes and in cats with CHF.

(J Vet Emerg Crit Care 2012; 22(4): 398–408) doi: 10.1111/j.1476-4431.2012.00768.x

Keywords: cardiotonic agents, phosphodiesterase inhibitors, pyridazines, vasodilator agents

Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
cAMP	cyclic adenosine monophosphate
cGMP	guanosine 3′,5′-cyclic monophosphate
CHF	congestive heart failure
CS	Cocker Spaniel
CVHD	chronic valvular heart disease
DP	Doberman Pinschers
DCM	dilated cardiomyopathy
ISACHC	International Small Animal Cardiac Health Council
LA:Ao	left atrium to aorta ratio
LPS	lipopolysaccharide-stimulated
LVID	left ventricular internal diameter
NO	nitric oxide
NF-κB	nuclear factor κB
NYHA	New York Heart Association
PAP	pulmonary artery pressure
PDE3	phosphodiesterase 3
PKA	protein kinase
RAAS	renin-angiotensin-aldosterone system
RF	regurgitant fraction
TnC	cardiac troponin C
TRFV	tricuspid regurgitant flow velocity
TXA$_2$	thromboxane A$_2$
^{99m}Tc-DTPA	^{99m}Tc-diethylenetriamine-pentacetic acid

From the VCA All-Care Animal Referral Center, Fountain Valley, CA 92708.

Address correspondence and reprint requests to
Dr. Kimberly Boyle, VCA All-Care Animal Referral Center, 18440 Amistad Street, Fountain Valley, CA 92708, USA.
Email: kboyledvm@gmail.com

Introduction

Approximately 10% of dogs presenting to primary care veterinary practices have heart disease.[1] Mitral regurgitation caused by acquired chronic valvular heart disease (CVHD) is the most common cause of congestive heart failure (CHF) and cardiac-related mortality in dogs, accounting for 75% to 85% of canine cardiac disease.[1,2] Dilated cardiomyopathy (DCM) is a another well-recognized and serious cause of cardiac morbidity and mortality in the dog.[3] Pimobendan[a] is a newer drug that has been demonstrated to be safe and effective for the treatment of CHF secondary to CVHD or DCM in dogs.[4–6] This review of pimobendan will firstly focus on its dual mechanism of action then its impact on relevant cardiovascular physiology and includes review of the relevant literature to date.
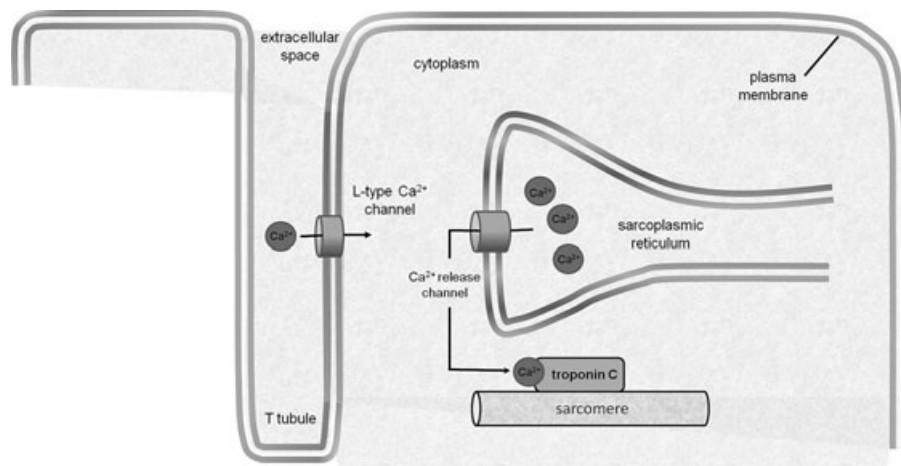
Figure 1: Cardiac myocyte. The influx of extracellular calcium through L-type calcium channels during excitation triggers the release of calcium from the sarcoplasmic reticulum. The increased cytosolic calcium activates contraction of the sarcomere myofilaments via binding of calcium to TnC.

Mechanism of Action

Pimobendan is an inodilator exerting an inotropic effect by a dual mechanism of action consisting of calcium sensitization and inhibition of phosphodiesterase 3 (PDE3) and exerting a vasodilatory effect via PDE3 inhibition. Traditional inotropic drugs such as cardiac glycosides and catecholamines possess narrow therapeutic margins of safety, limited oral bioavailability, and both increase cardiac energy requirements and provoke or exacerbate ventricular arrhythmias.[7–10] As a result, new agents have been investigated. Pimobendan is a benzimidazole-pyridazinone derivative approved by the US Food and Drug Administration (FDA) for treatment of CHF in dogs.[11] Because its mechanism of action is not dependent upon endogenous catecholamines, stimulation of cardiac β-adrenergic receptors, or inhibition of Na^+/K^+-ATPase, it is classified as a nonsympathomimetic, nonglycoside inotropic drug.[11] The principle mechanisms by which pimobendan exerts its clinical effects are discussed below.

Calcium sensitization, the predominant inotropic effect of pimobendan in the failing heart, involves increasing the affinity of the cardiac troponin C (TnC) regulatory site for calcium (Figure 1).[12–17] TnC is the calcium binding subunit of the myofibrillar troponin-tropomyosin regulatory system. The binding of calcium to TnC leads to activation of the myofibrillar protein interaction, force generation, and myocardial contraction. The degree of activation, and therefore strength of contraction, is directly correlated to the concentration of cytosolic free calcium as well as its binding affinity for TnC.

Positive inotropy is also achieved via pimobendan's PDE3 inhibitory effects within cardiac myocytes (Figure 2).[18] The net effect of PDE3 inhibition is an increase in cyclic adenosine monophosphate (cAMP), which is the most important second messenger in cardiac myocytes.[18,20] Stimulation of many cells occurs through activation of G-protein-linked receptors located on their membrane. This leads to activation of G proteins that signal and regulate the production of cAMP.[21] In most cells, cAMP activates cAMP-dependent protein kinase (PKA) which catalyzes the transfer of terminal phosphate groups from ATP to specific substrates. To maintain balance of cAMP, removal is accomplished by PDEs that hydrolyze cAMP phosphodiester bonds.[22] Of the 11 PDE families, those in the PDE3 and PDE5 families have clinically relevant roles in the cardiovascular system.[23] Pimobendan's PDE3 inhibition in cardiac myocytes results in phosphorylation of several substrates (Figure 2).[24–28] Phosphorylation of phospholamban increases calcium sequestration by the sarcoplasmic reticulum during diastole. Phosphorylation of calcium release channels causes increased release of calcium by the sarcoplasmic reticulum during systole. Phosphorylation of L-type calcium channels increases calcium influx during systole. Each of these PDE3 inhibitory mediated effects contributes to positive inotropy.

Pimobendan's active metabolite, UD-CG 212 Cl, has been shown to be a competitive antagonist for A_1-adenosine receptors, which is a less commonly recognized contributor to increased inotropy.[29] A_1-adenosine receptors are ubiquitous throughout the body and have an inhibitory function in most tissues. Blocking the inhibitory effects of A_1-adenosine receptor stimulation in the heart leads to cAMP synthesis and positive inotropy.[29,30]

The PDE3 inhibitory action of pimobendan is largely responsible for the positive inotropic effect in the healthy
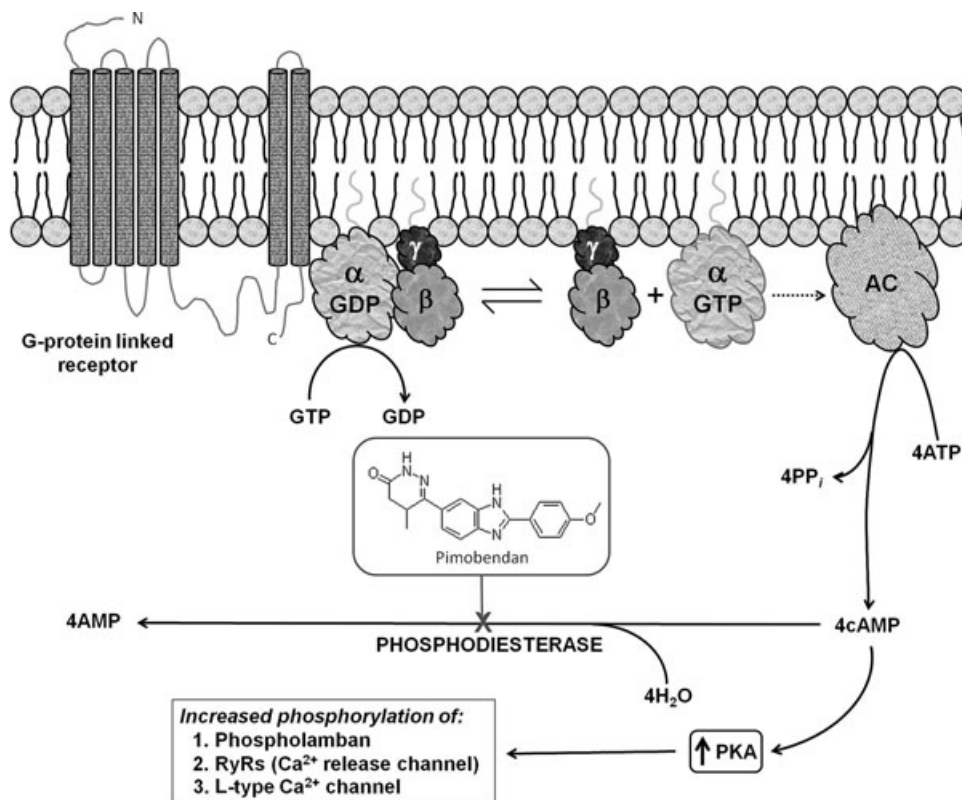
Figure 2: Signal transduction: G-Protein, cAMP, PKA, and PDEs. Binding of a signaling molecule to G-protein linked receptors leads to activation of GTP binding proteins (G proteins). The G protein binds to the catalytic subunit, adenyl cyclase (AC), which allows ATP to be hydrolyzed to cAMP. PKA is activated by cAMP. The activated PKA phosphorylates target proteins. Cyclic nucleotide PDE converts cAMP to AMP, thus reducing the amount of cAMP that can activate PKA. Pimobendan, a PDE inhibitor, prevents breakdown of cAMP, increasing PKA and protein phosphorylation.

heart. In the failing heart some studies indicate that it is the calcium sensitizing effects that predominate.[16,17] Calcium sensitization has pharmacologic benefits over other inotropic agents, such as digitalis and catecholamines, which increase cytosolic calcium concentrations. Increasing cytosolic calcium is associated with risks of calcium overload, increased myocardial oxygen consumption, and arrhythmias.[31] Moreover, the positive inotropic effects of catecholamines are often rapidly lost during chronic administration due to β-adrenergic receptor down regulation.[32]

In addition to positive inotropy, pimobendan results in both arterial and venodilation.[33–37] These effects are mediated via inhibition of PDE in vascular smooth muscle cells, which increases cAMP and guanosine 3′,5′-cyclic monophosphate (cGMP), two enzyme systems that play pivotal roles in maintenance of vascular smooth muscles cells.[38,39] Increasing cAMP and cGMP in vascular smooth muscle facilitates calcium uptake by intracellular storage sites thereby decreasing the amount of calcium available for contraction.[39] The end result is vasodilation of both systemic and pulmonary vascular

beds via smooth muscle relaxation. Although the venodilating effects have been shown in some species to be more pronounced than the arterial dilation, pimobendan is generally considered to have balanced vasodilatory effects.[34–36, 40–42]

Additional Pharmacological Effects

Effects on the immune system
Pimobendan has been shown to have beneficial effects on the immune system in multiple ways and in various species. Pimobendan has been shown to have a therapeutic effect in the acute stage of viral myocarditis in murine models.[43] This is mediated in part by inhibition of proinflammatory cytokines and inhibition of the synthesis of nitric oxide (NO) by inducible NO synthase.[43] The ability of PDE inhibitors to suppress production of NO was further investigated in cultured macrophages. Pimobendan was the most potent inhibitor of nitrite accumulation.[44] Pimobendan also inhibited the activity of transcription factor nuclear factor κB (NF-κB).[45] NF-κB regulates the expression of several genes (IL-1B, IL-6, TNF-α) involved

in immune and inflammatory responses and has been demonstrated in the myocardium of the failing human heart.[45] Reduction of NF-κB ameliorates the contribution of the immune system to heart failure.[45–47] Finally, exposure of lipopolysaccharide-stimulated (LPS) peripheral blood mononuclear cells to various concentrations of PDE inhibitors resulted in decreased LPS at all concentrations with pimobendan.[47] These effects of pimobendan on the immune system have yet to be demonstrated in dogs.

Effects on catecholamine secretion

CHF results in chronic activation of the sympathetic nervous system that can lead to deleterious effects. Pimobendan has been shown to reduce catecholamine synthesis and secretion in cultured adrenal medullary cells.[48] In vivo studies in dogs and people support the in vitro results. People with moderate, nonischemic heart failure receiving a regimen of digitalis, diuretics and an angiotensin-converting enzyme inhibitor (ACEI) were treated with pimobendan. After 3 months, plasma concentrations of norepinephrine improved in patients treated with pimobendan compared with the control group.[49] This improvement was sustained for 2 years. Dogs with mild mitral regurgitation treated with pimobendan for 4 weeks had significantly reduced plasma norepinephrine at the end of the study period.[50]

Antithrombotic effects

Platelet aggregation is highly regulated by cyclic nucleotides, particularly cAMP.[51,52] PDE3 inhibitors prevent aggregation of platelets via regulation of cAMP.[51,52] Pimobendan's antithrombotic activity has been demonstrated in both in vitro and in vivo studies. Pimobendan inhibited platelet aggregation and thromboxane A$_2$ (TXA$_2$) secretion in cultured endothelial cells, suggesting TXA$_2$-mediated antithrombotic properties.[53] Both spontaneous and collagen-induced aggregation were inhibited by pimobendan in a dose-dependent manner (0.5–10 mM) in human whole blood.[54] Pimobendan also inhibited platelet aggregation in platelet rich feline plasma.[55] In vivo studies have supported the in vitro results. Antithrombotic activity was demonstrated in dogs with recurrent thrombi in a partially stenosed coronary artery.[56] In a recent abstract, Shipley et al evaluated the in vitro effects of pimobendan on platelet aggregation using thromboelastography.[b] They found that pimobendan exerted a mild inhibitory effect on platelet aggregation in dogs. However, the concentration at which inhibition of platelet aggregation occurred, 10.0 mM, is roughly 1,000-fold higher than the clinically achievable concentration in dogs (0.01 mM).[d]

Effects on rhythm

Pimobendan prolongs the cardiac action potential that initially led to the thought that it may prolong myocardial refractoriness and decrease the tendency to induce re-entrant arrhythmias.[14,57,58] However, administration of pimobendan to anesthetized dogs led to a decrease in atrial, ventricular, and atrioventricular nodal refractory periods.[59] Furthermore, pimobendan was ineffective at preventing induction of ventricular tachycardia and failed to protect animals from developing ventricular fibrillation in a canine model of myocardial infarction.[60] While relevant to human patients who frequently suffer from ischemic heart disease, these data are less applicable to canine cardiac disease patients as they rarely suffer from acute myocardial infarction.

Insulinotropic effects

Similar intracellular signaling mechanisms exist in both cardiomyocytes and pancreatic β-cells. Calcium is involved in the contractile and exocytotic events of insulin release from β-cells. Therefore, the possible insulinotropic effect of pimobendan was examined in rat pancreatic β-cells.[61] It was demonstrated that via calcium sensitization pimobendan enhanced glucose-induced insulin release in a dose-dependent manner. This effect and its clinical relevance have not been studied in dogs.

Formulation and Pharmacokinetics

Pimobendan is FDA approved for the management of the symptoms of mild, moderate, or severe CHF in dogs due to CVHD or DCM.[c] It is indicated for use with concurrent therapy for CHF as appropriate on a case-by-case basis. Pimobendan is supplied as oblong, half-scored, chewable tablets in concentrations of 1.25 mg or 5 mg. Studies used to gain FDA approval demonstrated an increase in cardiac contractility in a dose-dependent manner up to a dose of 0.5 mg/kg.[b] Further studies supported a total daily dose of 0.4 to 0.6 mg/kg administered in 2 portions, not necessarily equal, approximately 12 hours apart.[b]

In people, pimobendan is readily distributed into tissues and peak onset of action is <1 hour after oral administration.[62,63] Although food decreases the aqueous solution of pimobendan, the effect of food on absorption from tablets is unknown.[b] Pimobendan undergoes hepatic demethylation via oxidation to a pharmacologically active metabolite (UD-CG 212 Cl).[62] Maximal mean plasma concentrations (Cmax) in dogs for pimobendan and UD-CG 212 Cl are 1–4 hours postdose (mean was 2 and 3 hours, respectively).[d] Plasma protein binding in dogs of both pimobendan and UD-CG 212 Cl are >90%.[c] UD-CG 212 Cl is conjugated with sulfate or glucuronic acid and excreted mainly in feces.[c] In people, only 5% of

pimobendan and its metabolites are eliminated via kidneys, which eliminates dosing concerns with concurrent azotemia.[64] The total body clearance of pimobendan is approximately 90 mL/min/kg, and the terminal elimination half-lives of pimobendan and UD-CG 212 Cl are approximately 0.5 hours and 2 hours, respectively.[c] Despite the short half-lives of the drugs, the pharmakodynamic effects in people are >8 hours.[65]

Preclinical Investigations

Numerous studies have reported the effects of pimobendan in vitro.[12–14,36,66,67] Studies on both intact and demembranated guinea pig and canine cardiac muscle demonstrated pimobendan increased calcium affinity (ie, calcium sensitization) of the regulatory binding sites of TnC.[12,14] Furthermore, patients with reduced ventricular function were more sensitive to these effects when compared with patients with normal ventricular function.[17] However, other data suggested that pimobendan's inotropic effect on the failing human myocardium was predominantly due to inhibition of PDE3.[68] Studies have also evaluated the mechanism of action of pimobendan's active metabolite. The PDE3 inhibitory action of UD-CG 212 Cl was significantly more potent than that of pimobendan.[69] Controversy exists as to whether UD-CG 212 Cl has calcium sensitizing properties.[69–72] Vascular properties have also been studied in vitro, indicating that the vasodilatory effect of pimobendan is due to an increase in cAMP resulting from PDE inhibition.[36] Additional studies have compared the mechanoenergetic effects of pimobendan with other inotropic agents, such as isoproterenol and dobutamine, and shown that for a given increase in myocardial contractility, the myocardial oxygen consumption was less for pimobendan.[66,73]

Results of in vivo investigations on the inotropic effectiveness of pimobendan in models of either ischemic or postischemic impairment of myocardial contractile function demonstrate that in the acute setting of compromised contractility and reduced cardiac output, pimobendan is able to improve contractility of the heart.[34,74,75] Cardiac function was assessed in anesthetized pigs with experimentally reduced blood flow.[34] Pimobendan increased both max LV dP/dt, an index used to characterize the contractile ability of the heart, and cardiac output.[34] Pretreatment with propranolol did not modify any of the cardiovascular responses of pimobendan, excluding involvement of β-adrenoceptor stimulation. Pimobendan increased survival by 27% in hamsters with a hereditary cardiomyopathy that results in pathology similar to ischemic heart diseases.[76] It is important to recognize that many experimental models are designed to mimic the common ischemic cardiovascular diseases of people that are rare in companion animals. A model of pacing-induced CHF was studied in 7 mongrel dogs comparing pimobendan to the pure PDE3 inhibitor, amrinone.[77] Prior to induction of CHF, these drugs produced equivalent inotropic and vasodilatory actions. After induction of CHF, amrinone's inotropic effects were attenuated whereas pimobendan's effects persisted. Despite a short-term study with a small sample size (4 beagles), results from Kanno et al[50] demonstrated that treatment of dogs with induced mild mitral regurgitation with pimobendan resulted in decreased systolic and mean blood pressure, decreased cardiac oxygen consumption, increased ejection fraction, increased fractional shortening, decreased regurgitant stroke volume, and a decreased left atrium to aorta (LA:AO) ratio.[50] In a number of animal models, pimobendan has been shown to dilate the venous and arterial vasculature.[34,35,41,78,79] However, differences in the potency of vasodilatory effects, based on degree of changes in mean arterial blood pressure or left ventricular end-diastolic blood pressure, have been reported, which may be due to the absence or presence of anesthesia as well as to species differences.

Multiple studies have been performed to evaluate the pharmacologic effects of pimobendan in healthy canine subjects.[80–83] A study of 23 open-chest, barbiturate-anesthetized mongrel dogs demonstrated that pimobendan increased heart rate, ejection fraction, and myocardial contractility.[83] A randomized, blinded, crossover study examined renal function in 10 clinically normal dogs receiving meloxicam and pimobendan alone or in combination for a 7-day period. Renal function was assessed by concentrations of blood urea, creatinine, sodium, potassium, and chloride as well as by glomerular filtration rate, which was measured by renal scintigraphy and plasma clearance of ^{99m}Tc-diethylenetriaminepentacetic acid (^{99m}Tc-DTPA). Results showed that alone or in combination, neither altered renal function in healthy dogs.[80] Another study in healthy dogs investigated the effects of pimobendan on the renin-angiotensin-aldosterone system (RAAS).[82] Other vasodilators activate the RAAS, however this did not occur in this study. The lack of vasodilatory-induced RAAS activation was attributed to positive inotropic maintenance of glomerular filtration.[82] This study also evaluated the effects of pimobendan on furosemide-treated dogs. As expected, furosemide activated the RAAS and concurrent administration of pimobendan did not diminish this activation.[82] The results of this study demonstrated that pimobendan is not a substitute for an ACEI.

Clinical Investigations

Data are limited regarding the use of pimobendan in dogs with asymptomatic CVHD (Table 1). A blinded,

Table 1: Summary of selected veterinary publications evaluating pimobendan in dogs with mitral valve disease

Study population	Type of study	Key findings	Reference
Asymptomatic CVHD			
24 client-owned dogs ISACHC Ib CVHD	Prospective Blinded Controlled	Pimobendan group: • No decrease in RF • Significant increase in the EF at 30 days • Nonsustained decrease in end systolic LVID	Ouellet et al. (2009)
12 nonclient-owned beagles NYHA class I CVHD	Prospective Double blinded Randomized Parallel group	Pimobendan group: • Decreased systolic LVID • Increased RF • Histologic grades of mitral valve lesions were more severe	Chetboul et al. (2007)
4 beagles Induced mild MR	Experimental	Pimobendan effects: • Increased cardiac contractility • Vasodilation • Reduced volumetric load of the LV and LA	Kanno et al. (2007)
2 Dogs Without echocardiographic exams On long-term pimobendan	Case report	Dog 1 (10-month treatment with pimobendan) and Dog 2 (5-month treatment with pimobendan) both with evidence of increased MR and myocardial hypertrophy, which resolved with cessation of pimobendan	Tissier et al. (2005)
Symptomatic CVHD			
252 client-owned dogs In CHF caused by CVHD Class not defined 124 treated w/pimobendan 128 treated w/benazepril	Prospective Single blinded Randomized	Compared with benazepril, pimobendan prolongs Time to: • Sudden death • Time to euthanasia for cardiac reasons • Treatment failure	Haggstrom et al. (2008)
76 client-owned dogs ISACHC Class II or III CVHD	Prospective Double blinded Randomized Controlled Multicentre	Pimobendan • Improvement in ISACHC class in 84% of dogs • Long-term median survival 415 days Benazepril • Improvement in ISACHC class in 56% of dogs • Long-term median survival 128 days	Lombard et al. (2006)
43 client-owned dogs NYHA class II or III CVHD	Prospective Single blinded Randomized Parallel group	Pimobendan group: • Well tolerated compared with ramipril • 25% as likely as ramipril dogs to have an adverse heart failure outcome	Smith et al. (2005)

RF, regurgitant fraction; EF, ejection fraction; LVID, left ventricular internal diameter; LV, left ventricle; LA, left atrium.

randomized, prospective study was performed on dogs with asymptomatic CVHD and compared the cardiac pharmacodynamics of long-term monotherapy with either pimobendan or benazepril.[84] The study objective was to determine whether the chronic use of either of these drugs at standard recommended dosages could produce cardiac lesions.[84] Inclusion was limited to dogs with evidence of cardiac disease but no clinical signs or exercise intolerance (ie, New York Heart Association (NYHA) class I). Dogs were not on any concurrent therapy. While a marked and sustained increase in systolic myocardial function was noted based on increased fractional shortening and decreased left ventricular systolic diameter, there was a concomitant and detrimental worsening of the mitral regurgitant jet and the development of jet lesions. A prospective, blinded, controlled clinical trial evaluated the effect of the addition of pimobendan on echocardiographic parameters in dogs with asymptomatic CVHD.[85] This study included 24 client-owned

dogs with an LA:Ao > 1.6 and no signs of CHF on thoracic radiographs. Permitted concurrent therapy included an ACEI. Echocardiographic evaluations were performed upon enrollment and at 30, 90, and 180 days. Results suggested that the addition of pimobendan did not decrease the regurgitant fraction (RF) over the study period. While there was a significant increase in the ejection fraction of the pimobendan-treated dogs at 30 days as well as a decrease in systolic left ventricular diameter, this improvement was not sustained over the 6-month trial period. This study did not identify beneficial long-term changes in the severity of mitral regurgitation after addition of pimobendan to ACEI treatment in dogs with asymptomatic CVHD.[85] Tissier et al[86] described 2 cases of dogs without prior echocardiographic examination that were treated with long-term pimobendan. Both dogs had evidence of myocardial hypertrophy and increased mitral valve regurgitation, which improved after discontinuation of pimobendan.[86]

Smith et al[87] first described the clinical efficacy and safety of pimobendan by comparing it with ramipril over a 6-month period in dogs with mild to moderate CHF caused by CVHD (Table 1).[87] All dogs were also treated with furosemide and digoxin was used on a case-by-case basis. Dogs in the ramipril group may have had more advanced disease at baseline confounding the results that dogs treated with pimobendan were 25% less likely to have an adverse heart failure outcome (eg, euthanized, died, or removed from the study as direct consequence of heart failure). The VetSCOPE study compared pimobendan and benazepril in 76 dogs with International Small Animal Cardiac Health Council (ISACHC) class II (ie, clinical signs with exertion or excitement) or III (ie, clinical signs at rest) heart failure caused by CVHD.[88] Furosemide and antiarrhythmic agents as needed were permitted, however the use of other ACEI and digoxin were not allowed. Long-term median survival for dogs receiving pimobendan was 415 days versus 128 days for dogs not on pimobendan. Due to ongoing controversy regarding the optimal treatment for dogs with CHF secondary to CVHD, the landmark QUEST study was designed to compare the use of pimobendan to that of benazepril. This was a prospective, multicenter, randomized, single-blinded, comparator study that included 252 client-owned dogs.[4] Permitted concurrent treatment included diuretics and digoxin but excluded ACEI. The study was prospectively designed to demonstrate a 50% difference in median times to reach the primary endpoint between the treatment groups. The primary endpoint was met when one of the following occurred: sudden cardiac death, euthanasia as a consequence of the cardiac disease, or treatment failure leading the clinician to withdraw the dog from the trial. While the proportion of dogs reaching the primary endpoint in the 2 groups was not different, the median time to reach the primary endpoint for dogs treated with pimobendan was almost twice as great (267 days) as for dogs treated with benazepril (140 days). These results demonstrate the superior effect of pimobendan for extending survival in dogs with CHF caused by CVHD when compared to benazepril. Moreover, being the largest prospective veterinary cardiovascular study with the highest recorded event rate, this study allowed for the most extensive analysis of covariates to date. In the multivariate analyses, after controlling for the effect of 33 other variables measured at baseline, pimobendan therapy continued to confer a significant risk reduction for reaching the primary endpoint compared with benazepril therapy. Seven other baseline variables had a significant favorable effect on the risk for reaching the primary endpoint: being a CKCS, receiving a lower daily furosemide dose, and having a better exercise tolerance, a lower VHS score, a lower LA/Ao ratio, a lower left ventricular internal diameters

(LVIDs), and a higher serum creatinine concentration. Despite the significance of the findings in the QUEST study, the study did not address the potential benefit of the combined therapy of pimobendan and an ACEI. Therefore, it should be emphasized that using pimobendan does not preclude the need for a simultaneous ACEI in the management of CHF.[82]

Consensus Statement of Guidelines for the Diagnosis and Treatment of Canine CVHD

In 2009, the American College of Veterinary Internal Medicine (ACVIM) Specialty of Cardiology published a consensus statement on guidelines for the diagnosis and treatment of canine CVHD.[89] For acute, hospital-based therapy of patients with current clinical signs of CHF, a consensus recommendation included the use of pimobendan (0.25–0.3 mg/kg PO q12h).[89] While evidence from clinical trials supporting the chronic use of pimobendan in the management of patients with CHF is stronger than for the acute situation, the recommendation to use pimobendan in acute heart failure therapy is supported by hemodynamic and experimental evidence as well as the collective anecdotal experience of the panelists. At home, long-term therapy for patients with past or current CHF included continuation of pimobendan. Patients with end-stage disease and clinical signs refractory to "standard therapy" should be receiving maximal tolerated doses of furosemide, an ACEI, and pimobendan. Pimobendan is not recommended in patients at high risk for developing heart disease that currently have no identifiable structural disorder or for patients with structural heart disease that have not yet developed clinical signs. Therapy for asymptomatic patients with hemodynamically significant valve regurgitation, as evidenced by radiographic or echocardiographic findings of left-sided heart enlargement was controversial, and no consensus could be reached with currently available evidence.

CHF caused by DCM

While occult DCM can have a protracted silent course, overt DCM can be a devastating disease. The clinical course of DCM is different among affected breeds with Doberman Pinschers (DPs) having a poorer prognosis.[3] Two prospective, double-blinded, randomized, placebo-controlled studies have been performed that evaluated the safety and effectiveness of pimobendan for CHF due to DCM (Table 2).[5,6] These studies supported the approval of pimobendan for use in this setting. Fuentes et al[5] evaluated pimobendan in 2 breeds commonly affected with DCM, DPs, and Cocker Spaniels (CSs).[5] Inclusion criteria included echocardiographic

Table 2: Summary of selected publications evaluating pimobendan in dogs with DCM

Study population	Type of study	Key findings	Reference
367 Dogs with DCM ISACHC Class 1, 2, or 3	Retrospective study of prognostic factors	Pimobendan was: • Administered to 30% of dogs • Used more frequently in dogs with more advanced disease • Not significantly associated with use and survival • Not available during entire study period	Martin et al. (2010)
16 DPs With CHF caused by DCM Class not defined	Prospective Double blind Randomized Placebo controlled	Pimobendan-treated dogs had a significant improvement in time to treatment failure compared with placebo	O'Grady et al. (2008)
10 DPs 10 CSs Modified NYHA class 3 or 4	Prospective Double blind Randomized Placebo controlled	Addition of pimobendan to traditional therapy improved functional heart failure class in both DPs and CSs and significantly increased survival in DPs	Fuentes et al. (2002)

DPs, Doberman Pinschers; CSs, Cocker Spaniels.

confirmation of a dilated, hypocontractile left ventricle in the absence of marked valvular disease or congenital heart defects and radiographic evidence of pulmonary edema. The subjects were randomized to receive either pimobendan or placebo. Permitted background therapy included furosemide, enalapril, and digoxin. The median survival time for pimobendan-treated CSs was 1,037 days compared with 537 days for the placebo group. The median survival time for pimobendan-treated DPs was 329 days compared with 50 days for the placebo group. Placebo-treated DPs had a greater number of dogs with atrial fibrillation at baseline compared with pimobendan-treated DPs. Given that atrial fibrillation in DPs with DCM is associated with a poorer prognosis, future studies should consider separate randomization for dogs with atrial fibrillation.[90] Overall, the results of this study indicated that in both breeds the addition of pimobendan to standard treatment (eg, furosemide, enalapril, digoxin) resulted in significant improvement in functional heart failure class.[5] These findings were supported by a study of the effects of pimobendan on DPs diagnosed with CHF caused by DCM.[6] Sixteen DPs were randomized to receive either pimobendan (0.25 mg/kg PO q12) or placebo. Concurrent therapy including furosemide and benazepril hydrochloride was permitted. Despite randomization, at time 0, the pimobendan group had significantly greater echocardiographic ventricular dimensions suggesting more advanced heart failure than the placebo group. Regardless, the addition of pimobendan to traditional diuretic and ACEI therapy significantly increased survival in DPs with CHF caused by DCM with a time to treatment failure (survival time to death) of 130.5 days for the pimobendan-treated group compared with 14 days for placebo.[6] A recent retrospective study of 367 cases of canine DCM examined the prognosis and its association with clinical presentation, diagnostic findings,

and drug use.[3] Regarding the use of pimobendan, this study showed that the frequency of its use increased with higher ISACHC heart failure class. In this study, the use of pimobendan was not significantly associated with survival. However, given the nature of a retrospective study, it is difficult to make associations between drugs and survival; moreover, in 1993, the beginning of the study period and throughout a significant portion of the study period, pimobendan was not available for use further confounding the study results.

Pulmonary Hypertension

PDE inhibitors are being used therapeutically to treat pulmonary arterial hypertension (PAH). Studies in rats with PAH suggest a reduced sensitivity of pulmonary arteries to certain vasodilators, which might be due in part to increased PDE3 and PDE5.[91] This provides a possible molecular mechanism by which PDE inhibitors might exert their beneficial effects in cases of PAH.[91] The PDE5 inhibitor sildenafil is FDA approved and licensed for use in people with pulmonary hypertension and has shown to be effective at reducing pulmonary artery pressure (PAP) in dogs.[e,92] In a study of 10 client-owned dogs diagnosed with PAH secondary to CVHD, treatment with pimobendan was compared with placebo. Inclusion criteria included dogs with a tricuspid regurgitation jet yielding a peak tricuspid regurgitant flow velocity (TRFV) ≥ 3.5 m/s. Continuous wave Doppler was used to estimate the PAP by measuring the peak TRFV across the tricuspid valve and converting it to a pressure gradient by use of the modified Bernoulli equation.[93] In both short-term and long-term comparison, the use of pimobendan resulted in a decrease in peak TRFV.[94] The efficacy of pimobendan for the treatment of canine PAH secondary to disease processes other than CVHD have not been studied.

Pimobendan in Cats

There are minimal published data regarding the use of pimobendan in cats. A recent abstract presented data from a single oral dose study in cats.[f] These results indicated that pimobendan is rapidly absorbed in healthy cats and was characterized by a C max more than 4× higher than what has been described in dogs. Also, cats had an elimination half-life approximately 3× longer than what has been reported in dogs. Another recent abstract reported on the use of pimobendan in a population of client-owned cats with naturally occurring heart disease.[g] Medical records from 3 institutions revealed 161 client-owned cats who had received pimobendan for various disease processes: hypertrophic cardiomyopathy (62 cats), unclassified cardiomyopathy (55 cats), DCM (27 cats), and various non-CHF indications (17). The median dose of pimobendan used was 0.23 mg/kg q 12h and the median survival of cats was 102 days. Further prospective studies are warranted to determine if pimobendan has a role in treating CHF in cats. Finally, positive inotropic agents will increase the severity of systolic anterior motion of mitral valve and worsen end-systolic cavity obliteration; therefore, the use of pimobendan in cats with hypertrophic obstructive cardiomyopathy is contraindicated.

Conclusions

Pimobendan, an inodilator with calcium sensitizing and PDE3 inhibitory properties, has emerged as an important component of the modern standard of care for the management of CHF in dogs suffering from CVHD and DCM. Its use is supported by current expert-derived treatment guidelines and is FDA approved for these indications. Greater usage of pimobendan in veterinary medicine warrants further study to establish the safety and efficacy of this agent in other clinical settings such as asymptomatic myocardial diseases as well as CHF from all other causes. Emerging data in asymptomatic CVHD and PAH need to be confirmed with large, controlled studies. Recent data in cats indicate that pimobendan is being explored as a therapeutic modality in the management of feline CHF. Appropriate studies should be performed to establish the safety and efficacy of this drug in this species.

Footnotes

a Vetmedin, Boehringer-ingleheim, Ingelheim, Germany.
b FDA Freedom of Information Summary [United States Food and Drug Administration (FDA), Center for Veterinary Medicine (2007)] Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/2007–141-273-fois001.pdf. Accessed Oct 1, 2010.
c Veterinary Medicine Labels. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5441e5b2-cdc0–477a-bd9a-ec5f8d912281. Accessed Jul 15, 2011.
d Shipley EA, Hogan DF, Green HW, et al. Effect of pimobendan on platelet aggregation in dogs. J Vet Intern Med 2011; 25(3):632–767.
e Revatio, Pfizer, New York City, NY.
f Hanzlicek A, Margiocco M, Gehring R, et al. Pharmacokinetics of oral pimobendan in healthy cats: a single dose study. J Vet Intern Med 2010; 24(6):1537–1576. g. MacGregor JM, Rush JE, Laste N, et al. Use of pimobendan in 161 cats (2006–2009). J Vet Intern Med 2010; 24(3):660–795.

References

1. Atkins C, Bonagura J, Ettinger S, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. J Vet Intern Med 2009; 23(6):1142–1150.
2. Haggstrom J, Hoglund K, Borgarelli M. An update on treatment and prognostic indicators in canine myxomatous mitral valve disease. J Small Anim Pract 2009; 50(Suppl 1):25–33.
3. Martin MW, Stafford Johnson MJ, Strehlau G, et al. Canine dilated cardiomyopathy: a retrospective study of prognostic findings in 367 clinical cases. J Small Anim Pract 2010; 51(8):428–436.
4. Haggstrom J, Boswood A, O'Grady M, et al. Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. J Vet Intern Med 2008; 22(5):1124–1135.
5. Fuentes VL, Corcoran B, French A, et al. A double-blind, randomized, placebo-controlled study of pimobendan in dogs with dilated cardiomyopathy. J Vet Intern Med 2002; 16(3):255–261.
6. O'Grady MR, Minors SL, O'Sullivan ML, et al. Effect of pimobendan on case fatality rate in Doberman Pinschers with congestive heart failure caused by dilated cardiomyopathy. J Vet Intern Med 2008; 22(4):897–904.
7. Rogers NM, Jones TE, Morris RG. Frequently discordant results from therapeutic drug monitoring for digoxin: clinical confusion for the prescriber. Intern Med J 2010; 40(1):52–56.
8. Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. Am Heart J 2002; 144(6):1102–1108.
9. Singh RB, Dube GP, Dube KP, et al. Cardiac manifestations of digoxin intoxication. (Clinical correlations with serum levels). Acta Cardiol 1975; 30(2):85–91.
10. Beanlands RS, Bach DS, Raylman R, et al. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. J Am Coll Cardiol 1993; 22(5):1389–1398.
11. Kitzen J, Winbury M. Pimobendan. Cardiovascular Drug Reviews 1989; 6(4):265–291.
12. Solaro RJ, Fujino K, Sperelakis N. The positive inotropic effect of pimobendan involves stereospecific increases in the calcium sensitivity of cardiac myofilaments. J Cardiovasc Pharmacol 1989; 14(Suppl 2):S7–S12.
13. Ruegg JC, Pfitzer G, Eubler D, et al. Effect on contractility of skinned fibres from mammalian heart and smooth muscle by a new benzimidazole derivative, 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]-5-methy l-3(2H)- pyridazinone. Arzneimittelforschung 1984; 34(12):1736–1738.
14. Fujino K, Sperelakis N, Solaro RJ. Sensitization of dog and guinea pig heart myofilaments to Ca^{2+} activation and the inotropic effect of pimobendan: comparison with milrinone. Circ Res 1988; 63(5):911–922.
15. Ovaska M, Taskinen J. A model for human cardiac troponin C and for modulation of its Ca^{2+} affinity by drugs. Proteins 1991; 11(2):79–94.
16. Sato N, Asai K, Okumura S, et al. Mechanisms of desensitization to a PDE inhibitor (milrinone) in conscious dogs with heart failure. Am J Physiol 1999; 276(5 Pt 2):H1699–1705.

17. Scheld HH, Fritsche R, Schlepper M, et al. Pimobendan increases calcium sensitivity of skinned human papillary muscle fibers. J Clin Pharmacol 1989; 29(4):360–366.

18. Brunkhorst D, v der Leyen H, Meyer W, et al. Relation of positive inotropic and chronotropic effects of pimobendan, UD-CG 212 Cl, milrinone and other phosphodiesterase inhibitors to phosphodiesterase III inhibition in guinea-pig heart. Naunyn Schmiedebergs Arch Pharmacol 1989; 339(5):575–583.

19. Chen CH, Nakaya Y, Minami K, et al. Effects of pimobendan and its active metabolite, UD-CG 212 Cl, on Ca2+-activated K+ channels in vascular smooth-muscle cells. J Cardiovasc Pharmacol 1997; 30(6):739–743.

20. Hambleton R, Krall J, Tikishvili E, et al. Isoforms of cyclic nucleotide phosphodiesterase PDE3 and their contribution to cAMP hydrolytic activity in subcellular fractions of human myocardium. J Biol Chem 2005; 280(47):39168–39174.

21. Conti M, Jin SL. The molecular biology of cyclic nucleotide phosphodiesterases. Prog Nucleic Acid Res Mol Biol 1999; 63:1–38.

22. Wechsler J, Choi YH, Krall J, et al. Isoforms of cyclic nucleotide phosphodiesterase PDE3A in cardiac myocytes. J Biol Chem 2002; 277(41):38072–38078.

23. Stehlik J, Movsesian MA. Inhibitors of cyclic nucleotide phosphodiesterase 3 and 5 as therapeutic agents in heart failure. Expert Opin Investig Drugs 2006; 15(7):733–742.

24. James P, Inui M, Tada M, et al. Nature and site of phospholamban regulation of the Ca2+ pump of sarcoplasmic reticulum. Nature 1989; 342(6245):90–92.

25. Simmerman HK, Jones LR. Phospholamban: protein structure, mechanism of action, and role in cardiac function. Physiol Rev 1998; 78(4):921–947.

26. Seiler S, Wegener AD, Whang DD, et al. High molecular weight proteins in cardiac and skeletal muscle junctional sarcoplasmic reticulum vesicles bind calmodulin, are phosphorylated, and are degraded by Ca2+-activated protease. J Biol Chem 1984; 259(13):8550–8557.

27. Takasago T, Imagawa T, Shigekawa M. Phosphorylation of the cardiac ryanodine receptor by cAMP-dependent protein kinase. J Biochem 1989; 106(5):872–877.

28. Sculptoreanu A, Scheuer T, Catterall WA. Voltage-dependent potentiation of L-type Ca2+ channels due to phosphorylation by cAMP-dependent protein kinase. Nature 1993; 364(6434):240–243.

29. Parsons WJ, Ramkumar V, Stiles GL. The new cardiotonic agent sulmazole is an A1 adenosine receptor antagonist and functionally blocks the inhibitory regulator, Gi. Mol Pharmacol 1988; 33(4):441–448.

30. Ungerer M, Bohm M, Schwinger RH, et al. Antagonism of novel inotropic agents at A1 adenosine receptors and m-cholinoceptors in human myocardium. Naunyn Schmiedebergs Arch Pharmacol 1990; 341(6):577–585.

31. Endoh M. Cardiac Ca2+ signaling and Ca2+ sensitizers. Circ J 2008; 72(12):1915–1925.

32. Endoh M, Hori M. Acute heart failure: inotropic agents and their clinical uses. Expert Opin Pharmacother 2006; 7(16):2179–2202.

33. van Meel JC, Diederen W. Hemodynamic profile of the cardiotonic agent pimobendan. J Cardiovasc Pharmacol 1989; 14(Suppl 2):S1–6.

34. Verdouw PD, Hartog JM, Duncker DJ, et al. Cardiovascular profile of pimobendan, a benzimidazole-pyridazinone derivative with vasodilating and inotropic properties. Eur J Pharmacol 1986; 126(1–2):21–30.

35. Duncker DJ, van Dalen FJ, Hartog JM, et al. Usefulness of pimobendan in the treatment of heart failure. Arzneimittelforschung 1986; 36(12):1740–1744.

36. Fujimoto S, Matsuda T. Effects of pimobendan, a cardiotonic and vasodilating agent with phosphodiesterase inhibiting properties, on isolated arteries and veins of rats. J Pharmacol Exp Ther 1990; 252(3):1304–1311.

37. Tejerina T, Sesin J, Delgado C, et al. Effects of pimobendan and UD-CG-212 CL on calcium exchange and contraction in isolated rabbit aorta. Arch Int Pharmacodyn Ther 1990; 305:69–85.

38. Levy JH. Management of systemic and pulmonary hypertension. Tex Heart Inst J 2005; 32(4):467–471.

39. McDaniel NL, Rembold CM, Murphy RA. Cyclic nucleotide dependent relaxation in vascular smooth muscle. Can J Physiol Pharmacol 1994; 72(11):1380–1385.

40. Diederen W, Dammgen J, Kadatz R. Cardiovascular profile of UD-CG 115, a new orally and long acting cardiotonic compound, not related to beta-mimetics or cardiac glycosides. Naunyn-Schmiedebergs Arch Pharmac 1982; 321:141.

41. Duncker DJ, Hartog JM, Levinsky L, et al. Systemic haemodynamic actions of pimobendan (UD-CG 115 BS) and its O-demethylmetabolite UD-CG 212 Cl in the conscious pig. Br J Pharmacol 1987; 91(3):609–615.

42. Fujimoto S. Effects of pimobendan, its active metabolite UD-CG 212, and milrinone on isolated blood vessels. Eur J Pharmacol 1994; 265(3):159–166.

43. Iwasaki A, Matsumori A, Yamada T, et al. Pimobendan inhibits the production of proinflammatory cytokines and gene expression of inducible nitric oxide synthase in a murine model of viral myocarditis. J Am Coll Cardiol 1999; 33(5):1400–1407.

44. Matsumori A, Okada I, Shioi T, et al. Inotropic agents differentially inhibit the induction of nitric oxide synthase by endotoxin in cultured macrophages. Life Sci 1996; 59(10):PL121–125.

45. Wong S, Fukuchi M, Melnyk P, et al. Induction of cyclooxygenase-2 and activation of nuclear factor-kappa B in myocardium of patients with congestive heart failure. Circulation 1998; 98(2):100–103.

46. Sasayama S. Inotropic agents and immune modulation. Cardiovasc Drugs Ther 2002; 16(3):237–243.

47. Matsumori A, Ono K, Sato Y, et al. Differential modulation of cytokine production by drugs: implication for therapy in heart failure. J Mol Cell Cardiol 1996; 28:2491–2499.

48. Toyohira Y, Kubo T, Watanabe M, et al. Selective blockade of nicotinic acetylcholine receptors by pimobendan, a drug for the treatment of heart failure: reduction of catecholamine secretion and synthesis in adrenal medullary cells. Naunyn Schmiedebergs Arch Pharmacol 2005; 371(2):107–113.

49. Sasaki T, Kubo T, Komamura K, et al. Effects of long-term treatment with pimobendan on neurohumoral factors in patients with non-ischemic chronic moderate heart failure. J Cardiol 1999; 33(6):317–325.

50. Kanno N, Kuse H, Kawasaki M, et al. Effects of pimobendan for mitral valve regurgitation in dogs. J Vet Med Sci 2007; 69(4):373–377.

51. Blache D, Nargeot J, Nerbonne JM. Direct evidence for the inhibition of platelet aggregation and release by intracellular cyclic AMP produced with a new photoactivatable derivative. Thromb Haemost 1986; 55(2):168–172.

52. Feijge MA, Ansink K, Vanschoonbeek K, et al. Control of platelet activation by cyclic AMP turnover and cyclic nucleotide phosphodiesterase type-3. Biochem Pharmacol 2004; 67(8):1559–1567.

53. Eldor A, Vlodavsky I, Fuks Z, et al. Different effects of aspirin, dipyridamole and UD-CG 115 on platelet activation in a model of vascular injury: studies with extracellular matrix covered with endothelial cells. Thromb Haemost 1986; 56(3):333–339.

54. Saniabadi AR, Lowe GD, Belch JJ, et al. Platelet aggregation inhibitory effects of the new positive inotropic agents pimobendan and UD CG 212 in whole blood. Cardiovasc Res 1989; 23(3):184–190.

55. Bitterman H, Smith BA, Lefer AM. Use of the novel cardiotonic and vasodilator agent pimobendan in traumatic shock. Arzneimittelforschung 1988; 38(10):1389–1393.

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

57. Honerjager P, Heiss A, Schafer-Korting M, et al. UD-CG 115–a cardiotonic pyridazinone which elevates cyclic AMP and prolongs the action potential in guinea-pig papillary muscle. Naunyn Schmiedebergs Arch Pharmacol 1984; 325(3):259–269.

58. Wellens HJ, Brugada P, Farre J. Ventricular arrhythmias: mechanisms and actions of antiarrhythmic drugs. Am Heart J 1984; 107(5 Pt 2):1053–1057.

59. Kitzen JM, Lynch JJ, Driscoll EM, et al. Cardiac electrophysiologic and hemodynamic activity of pimobendan (UD-CG 115 BS), a new inotropic agent. J Pharmacol Exp Ther 1988; 244(3):929–939.

60. Lynch JJ, Kitzen JM, Hoff PT, et al. Effects of pimobendan (UD-CG 115 BS), a new positive inotropic agent, on ventricular tachycardia and ischemic ventricular fibrillation in a conscious canine model of recent myocardial infarction. J Cardiovasc Pharmacol 1988; 12(5):547–554.

61. Fujimoto S, Ishida H, Kato S, et al. The novel insulinotropic mechanism of pimobendan: direct enhancement of the exocytotic process of insulin secretory granules by increased Ca2+ sensitivity in beta-cells. Endocrinology 1998; 139(3):1133–1140.

62. Hagemeijer F, Roth W, Brand HJ. Correlations between the cardiovascular effects of pimobendan and plasma concentrations of the parent compound and of its major active metabolite, UD-CG 212 CL, in patients with congestive heart failure. J Cardiovasc Pharmacol 1989; 14(Suppl 2):S57–64.

63. Chu KM, Shieh SM, Hu OY. Plasma and red blood cell pharmacokinetics of pimobendan enantiomers in healthy Chinese. Eur J Clin Pharmacol 1995; 47(6):537–542.

64. Przechera M, Roth W, Kuhlkamp V, et al. Pharmacokinetic profile and tolerability of pimobendan in patients with terminal renal insufficiency. Eur J Clin Pharmacol 1991; 40(1):107–111.

65. Chu KM, Shieh SM, Hu OY. Pharmacokinetics and pharmacodynamics of enantiomers of pimobendan in patients with dilated cardiomyopathy and congestive heart failure after single and repeated oral dosing. Clin Pharmacol Ther 1995; 57(6):610–621.

66. Holubarsch C, Hasenfuss G, Just H, et al. Influence of the positive inotropic substance pimobendan (UD-CG 115 BS) on contractile economy of guinea pig papillary muscles. J Cardiovasc Pharmacol 1989; 14(Suppl 2):S13–17.

67. Wakisaka C, Kitamura N, Ohta T, et al. Effects of pimobendan, a new cardiotonic agent, on contractile responses in single skeletal muscle fibres of the frog. Fundam Clin Pharmacol 2000; 14(4):379–385.

68. Pagani E, O'Connor B, Allen P, et al. Effect of calcium binding protein modulators on myofibrillar MgATPase activity and cGMP-inhibitable phosphodiesterase activity from human cardiac muscle. Drug Development Research 1993; 29:195–202.

69. Bohm M, Morano I, Pieske B, et al. Contribution of cAMP-phosphodiesterase inhibition and sensitization of the contractile proteins for calcium to the inotropic effect of pimobendan in the failing human myocardium. Circ Res 1991; 68(3):689–701.

70. Endoh M, Shibasaki T, Satoh H, et al. Different mechanisms involved in the positive inotropic effects of benzimidazole derivative UD-CG 115 BS (pimobendan) and its demethylated metabolite UD-CG 212 Cl in canine ventricular myocardium. J Cardiovasc Pharmacol 1991; 17(3):365–375.

71. Komukai K, Kurihara S. Mechanisms of the inotropic effects of UD-CG 212 Cl, an active metabolite of pimobendan, on ferret papillary muscles. J Cardiovasc Pharmacol 1996; 27(5):673–679.

72. Van Meel JC, Entzeroth M, Redemann N, et al. Effects of pimobendan and its metabolite on myofibrillar calcium responsiveness and ATPase activity in the presence of inorganic phosphate. Arzneimittelforschung 1995; 45(2):136–141.

73. Hata K, Goto Y, Futaki S, et al. Mechanoenergetic effects of pimobendan in canine left ventricles. Comparison with dobutamine. Circulation 1992; 86(4):1291–1301.

74. Pouleur H, Gurne O, Hanet C, et al. Effects of pimobendan (UD-CG 115) on the contractile function of the normal and "postischemic" canine myocardium. J Cardiovasc Pharmacol 1988; 11(1):100–106.

75. Linder C, Diederen W, Van Meel J. Influence of pimobendan on isovolumic relaxation in dogs with normal heart function and with ischemic heart failure–comparison with milrinone. Naunyn Schmiedebergs Arch Pharmacol 1986; 334.

76. van Meel JC, Mauz AB, Wienen W, et al. Pimobendan increases survival of cardiomyopathic hamsters. J Cardiovasc Pharmacol 1989; 13(3):508–509.

77. Ohte N, Cheng CP, Suzuki M, et al. The cardiac effects of pimobendan (but not amrinone) are preserved at rest and during exercise in conscious dogs with pacing-induced heart failure. J Pharmacol Exp Ther 1997; 282(1):23–31.

78. Diederen W, Dammgen J, Kadatz R. Cardiovascular profile of UD-CG 115 BS, a new orally and long acting cardiotonic compound, not related to B-mimetics or cardiac glycosides. Naunyn Schmiedebergs Arch Pharmacol 1982; 321(suppl).

79. von Meel JC. Cardiovascular effects of the positive inotropic agents pimobendan and sulmazole in vivo. Arzneimittelforschung 1985; 35(1A):284–288.

80. Fusellier M, Desfontis JC, Le Roux A, et al. Effect of short-term treatment with meloxicam and pimobendan on the renal function in healthy beagle dogs. J Vet Pharmacol Ther 2008; 31(2):150–155.

81. Pagel PS, Hettrick DA, Warltier DC. Influence of levosimendan, pimobendan, and milrinone on the regional distribution of cardiac output in anaesthetized dogs. Br J Pharmacol 1996; 119(3):609–615.

82. Sayer MB, Atkins CE, Fujii Y, et al. Acute effect of pimobendan and furosemide on the circulating renin-angiotensin-aldosterone system in healthy dogs. J Vet Intern Med 2009; 23(5):1003–1006.

83. Pagel PS, Hettrick DA, Warltier DC. Comparison of the effects of levosimendan, pimobendan, and milrinone on canine left ventricular-arterial coupling and mechanical efficiency. Basic Res Cardiol 1996; 91(4):296–307.

84. Chetboul V, Lefebvre HP, Sampedrano CC, et al. Comparative adverse cardiac effects of pimobendan and benazepril monotherapy in dogs with mild degenerative mitral valve disease: a prospective, controlled, blinded, and randomized study. J Vet Intern Med 2007; 21(4):742–753.

85. Ouellet M, Belanger MC, Difruscia R, et al. Effect of pimobendan on echocardiographic values in dogs with asymptomatic mitral valve disease. J Vet Intern Med 2009; 23(2):258–263.

86. Tissier R, Chetboul V, Moraillon R, et al. Increased mitral valve regurgitation and myocardial hypertrophy in two dogs with long-term pimobendan therapy. Cardiovasc Toxicol 2005; 5(1):43–51.

87. Smith PJ, French AT, Van Israel N, et al. Efficacy and safety of pimobendan in canine heart failure caused by myxomatous mitral valve disease. J Small Anim Pract 2005; 46(3):121–130.

88. Lombard CW, Jons O, Bussadori CM. Clinical efficacy of pimobendan versus benazepril for the treatment of acquired atrioventricular valvular disease in dogs. J Am Anim Hosp Assoc 2006; 42(4):249–261.

89. Atkins C, Bonagura J, Ettinger A, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. J Vet Intern Med 2009; 23(11):1142–1150.

90. Calvert CA, Pickus CW, Jacobs GJ, et al. Signalment, survival, and prognostic factors in Doberman pinschers with end-stage cardiomyopathy. J Vet Intern Med 1997; 11(6):323–326.

91. Murray F, MacLean MR, Pyne NJ. Increased expression of the cGMP-inhibited cAMP-specific (PDE3) and cGMP binding cGMP-specific (PDE5) phosphodiesterases in models of pulmonary hypertension. Br J Pharmacol 2002; 137(8):1187–1194.

92. Bach JF, Rozanski EA, MacGregor J, et al. Retrospective evaluation of sildenafil citrate as a therapy for pulmonary hypertension in dogs. J Vet Intern Med 2006; 20(5):1132–1135.

93. Laaban JP, Diebold B, Zelinski R, et al. Noninvasive estimation of systolic pulmonary artery pressure using Doppler echocardiography in patients with chronic obstructive pulmonary disease. Chest 1989; 96(6):1258–1262.

94. Atkinson KJ, Fine DM, Thombs LA, et al. Evaluation of pimobendan and N-terminal probrain natriuretic peptide in the treatment of pulmonary hypertension secondary to degenerative mitral valve disease in dogs. J Vet Intern Med 2009; 23(6):1190–1196.