Pearls of Veterinary Practice

Pimobendan in Heart Failure Therapy – A Silver Bullet?

Pimobendan is a novel agent with properties that are highly desirable in the clinical management of congestive heart failure (CHF) secondary to both dilated cardiomyopathy (DCM) and chronic degenerative valvular disease in dogs. Review of available data suggests that pimobendan is safe, well tolerated, and leads to enhanced quality of life in dogs with CHF secondary to DCM or chronic valvular disease when used in combination with furosemide or other conventional therapies (e.g., angiotensin-converting enzyme inhibitors, digoxin). Pimobendan leads to a reduction in mortality from CHF associated with DCM, and ongoing studies are evaluating its effects on mortality associated with chronic valvular disease. **J Am Anim Hosp Assoc 2006;42:90-93.**

Sonya G. Gordon, DVM, DVSc, Diplomate ACVIM (Cardiology)

Matthew W. Miller, DVM, MS, Diplomate ACVIM (Cardiology)

Ashley B. Saunders, DVM, Diplomate ACVIM (Cardiology)

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Science, Texas A&M University, College Station, Texas 77843-4474.

Introduction

Many dogs with congestive heart failure (CHF) secondary to chronic degenerative atrioventricular valvular disease and dilated cardiomyopathy (DCM) enjoy a good quality of life while receiving conventional therapies such as furosemide and angiotensin-converting enzyme (ACE) inhibitors, with or without digoxin.[1] Affected dogs still have a poor long-term prognosis, however.[2,3] These dogs may die suddenly from arrhythmias, but, more often, death results from euthanasia following progressive deterioration of the quality of life. The most common reason for impaired quality of life is either failure to keep the dog free of signs of congestion with appropriate diuresis (with or without periodic abdominocentesis) or the development of severe signs of forward heart failure (e.g., marked exercise intolerance, lethargy, collapse, syncope, progressive renal insufficiency). Additionally, in dogs with chronic valvular disease, clinical signs of forward heart failure may be exacerbated by the development of pulmonary artery hypertension. Affected dogs often meet these endpoints, because the required level of diuresis is either inadequate or no longer tolerated. To reduce mortality in these dogs, applied medications must significantly reduce the morbidity associated with the common clinical signs of progressive CHF.

Background

Pimobendan is a benzimidazole pyridazinone derivative and is classified as an inodilator (i.e., positive inotrope and arteriovenous dilator).[4]

In failing hearts, it exerts its positive inotropic effects primarily through sensitization of the cardiac contractile apparatus to intracellular calcium.[5] As a phosphodiesterase (PDE) III inhibitor, it can potentially increase intracellular calcium concentration and increase myocardial oxygen consumption. However, the cardiac PDE effects of pimobendan are reportedly minimal at pharmacological doses in dogs with heart disease, which is a major advantage relative to other inotropic PDE inhibitors such as milrinone.[5,6] Pimobendan's calcium sensitization of the contractile apparatus is achieved by enhancement of the interaction between calcium and the troponin C complex, resulting in a positive inotropic effect that does not increase myocardial oxygen consumption.[7] Overall, pimobendan enhances systolic function by improving the efficiency of contraction and by limiting the arrhythmogenic side effects of other positive inotropes having a sole mechanism of action of increasing myocardial intracellular calcium.[5-7] Calcium sensitizers such as pimobendan may represent a class of inotropic agents that "safely" augment contractility.

Phosphodiesterase III and V are found in vascular smooth muscle.[8] Inhibitors of PDE III and V, such as pimobendan, lead to vasodilatation and reduction of both cardiac preload and afterload, which are the cornerstones of therapy in CHF. In addition, PDE V concentrations may be higher in the vascular smooth muscle of pulmonary arteries, so nonselective PDE inhibition may help ameliorate elevations in pulmonary artery pressure that tend to parallel long-standing elevations in left atrial pressure.

The significance of alterations in proinflammatory cytokines, such as tumor necrosis factor-α and interleukins 1-β and 6, on the progression of heart failure has been documented in many forms of heart disease.[9] Alterations in these cytokines are associated with increased morbidity and mortality. Pimobendan has demonstrated beneficial modulation of several such cytokines in various models of heart failure, which is an additional desirable property.[10,11]

Therapeutic Rationale

Tolerable reductions in cardiac preload and afterload through venous and arterial dilatation, respectively, are desirable in dogs with CHF secondary to either chronic valvular disease or DCM. The usefulness of "safe" augmentation of contractility is obvious in DCM (because it is characterized by global systolic dysfunction), but it is not so obvious in cases of valvular disease. Dogs with chronic valvular disease develop compensatory left ventricular (LV) remodeling in the form of eccentric hypertrophy (dilatation). Systolic function is often thought to be preserved until relatively late in the course of the disease, based on normal or exuberant echocardiographic surrogates of ventricular ejection, such as fractional shortening.[12] Interrogation of cardiac function by more sophisticated techniques has demonstrated reductions in LV systolic function in both an experimental canine model of mitral regurgitation (MR) and in chronic primary MR of humans, a condition very similar to chronic valvular disease of the dog.[10,13,14]

Impaired systolic function in cases of CHF secondary to valvular disease may contribute significantly to clinical signs of lethargy and exercise intolerance from reduced forward cardiac output. Although diuretics can relieve signs of congestion, they do little to alleviate and may exacerbate signs of forward failure. Traditionally, animals with CHF have been managed with judicious afterload-reducing agents such as ACE-inhibitors and/or more potent arteriolar dilators (i.e., hydralazine, amlodipine). These agents attempt to reduce the differential in pressure between the periphery and the left atrium, thereby reducing regurgitant flow and augmenting forward cardiac output.[15] However, dogs with advanced valvular disease often do not tolerate afterload reduction well. Frequently, clinical signs of forward heart failure do not resolve and may be exacerbated by afterload reduction, further impairing quality of life. Additionally, many dogs with advanced valvular disease and DCM have severe cardiomegaly leading to mitral annular dilatation, which contributes to secondary functional MR. Other therapies for chronic valvular disease involve surgical mitral valve repair and mitral annuloplasty; however, these therapies are not routinely available or performed in dogs. Furthermore, many dogs with advanced cardiac disease or other concurrent serious diseases, such as renal insufficiency, are not good candidates for open-heart surgery, even if clients wish to pursue this option.

If a potent positive inotropic agent could enhance mitral annular and LV papillary tone, thereby optimizing LV and mitral apparatus geometry, functional MR might be reduced with augmentation of forward cardiac output, thereby making any concurrent reductions in afterload better tolerated. This combined mechanism of action could be considered a pharmacological annuloplasty. Reductions in regurgitant fraction may also result in beneficial reverse remodeling (i.e., reduction in size) of the left ventricle and left atrium. This constellation of hemodynamic effects may also indirectly modulate neurohormonal systems responsible for the progression of heart failure.[16]

Safety and Efficacy

The efficacy of pimobendan in the treatment of CHF arising from DCM and chronic valvular disease has been evaluated more thoroughly than any other cardioactive medication to date, including ACE-inhibitors.[1-3,17-22] Available prospective data overwhelmingly support its ability to significantly reduce morbidity in dogs with CHF secondary to these conditions.[7-11] O'Grady *et al*. demonstrated a doubling of overall survival times in Doberman pinschers with CHF secondary to DCM, from 63±14 days (mean ± standard deviation) with furosemide, an ACE-inhibitor, and placebo, to 128±29 days with furosemide, an ACE-inhibitor, and pimobendan at 0.25 mg/kg per os (PO) *q* 12 hours (P=0.04).[19] Additional studies suggest a survival benefit with the combination of pimobendan and furosemide when compared to an ACE-inhibitor and furosemide (with or without digoxin) in dogs with CHF secondary to DCM or chronic valvular disease.[20,21] Other

studies offer conflicting evidence with respect to the superiority of pimobendan for the treatment of CHF secondary to valvular disease.[21,22] Preliminary analysis of an ongoing study by O'Grady *et al*. showed no survival advantage using pimobendan and furosemide compared to an ACE-inhibitor and furosemide in dogs with valvular-induced CHF.[22] Conversely, Smith *et al*. demonstrated a significant reduction of overall adverse outcomes, including death from the CHF (euthanized or died) and treatment failure when furosemide and ramipril (48%) were compared to furosemide and pimobendan (18%) over 6 months of treatment.[22] In both studies, no significant adverse consequences occurred, which suggested that the combination of pimobendan and furosemide may be as effective as furosemide and an ACE-inhibitor in treating CHF secondary to valvular disease.

To date, pimobendan appears to be safe and well tolerated in dogs with CHF associated with valvular disease. Pimobendan has not been prospectively evaluated, however, when used with conventional therapy, such as an ACE-inhibitor, furosemide, digoxin, spironolactone, etc. The authors have been using pimobendan (0.25 to 0.3 mg/kg PO *q* 12 hours) in addition to conventional therapy for >4 years in over 250 dogs for the treatment of CHF from both DCM and chronic valvular disease. Survival times and hemodynamic effects were reviewed in a subset of dogs with advanced CHF from valvular disease. In addition to pimobendan, these dogs received furosemide (100%, at least 3 mg/kg PO *q* 12 hours), an ACE-inhibitor (100%), spironolactone (>75%), a beta-blocker (20%), digoxin (11%), and hydrochlorothiazide (3%). Hemodynamic effects were evaluated prior to initiation of pimobendan and approximately 45 days later. No significant changes in indirect systemic blood pressures, body weight, hematocrit, total solids, serum creatinine, or electrolytes (P=0.05) were detected. Blood urea nitrogen (BUN) increased significantly in some dogs (mean pre-pimobendan BUN of 29 mg/dL versus post-pimobendan BUN of 33 mg/dL; P<0.05).

Heart and respiratory rates were reduced, and no changes occurred in the combined frequency of arrhythmias (i.e., ventricular premature beats, ventricular tachycardia, supraventricular premature beats, supraventricular tachycardia, and atrial fibrillation) on electrocardiograms. A trend (P=0.059) was noted in the reduction of dosage of furosemide administered to the dogs. Select echocardiographic parameters suggested improvement in systolic function, specifically reduction in LV internal dimension in systole, reduction of LV end-systolic area, and an increase in the percentage of LV area shortening. Reduction in the regurgitant fraction was suggested by a decrease in the radiographic vertebral heart score, a reduction in systolic left atrial diameter on echocardiography, and a decrease in the M-mode-derived ratio of left atrial to aortic size. Taken together, these findings suggested that the addition of pimobendan to conventional therapy involved no negative side effects and enhanced systolic function, as well as reduced filling pressures. Although these beneficial effects were observed (on average) 45 days after initiating pimobendan, more recent experience and pilot data suggest that these effects may be apparent as early as 24 hours, indicating a potential application in the treatment of acute, decompensated CHF. The median survival time of the dogs in the authors' 4-year study was 17 months (range 2 to 50 months). The median was estimated from a Kaplan-Meier survival curve where mortality was the outcome variable and dogs were censored (30%) if still alive at the time of analysis.

The authors' clinical experience is in agreement with available prospective data supporting the efficacy of adjunctive pimobendan therapy in improving the quality and length of life in dogs with CHF arising from both valvular disease and DCM. Pimobendan seems to be easy to use, requires no additional monitoring, and enjoys excellent client compliance. Pimobendan works very rapidly and can be used during the initial, acute phase of treating heart failure. Peak hemodynamic effects following oral administration on an empty stomach are achieved in 1 hour and last 8 to 12 hours.[4] The rapid onset of action, low rate of side effects, and decreased time of hospitalization with use of the drug have had a great impact on the willingness of clients to pursue the treatment of heart failure, as well as overall client satisfaction with the therapy. Hopefully, ongoing studies will further define any survival benefits associated with using pimobendan in dogs with valvular-induced CHF.

Pimobendan has been licensed for use in dogs with CHF since 2000 in many countries around the world, including Europe, Great Britain, Australia, Canada, and Mexico.[23] Pimobendan is produced and marketed by Boehringer Ingleheim under the trade name Vetmedin. A licensing study is currently under review in the United States, with an optimistic forecast for release of the drug early in 2007. Until such time that pimobendan is licensed in the United States, it can be legally imported on a case-by-case basis with permission from the Federal Drug Administration.

Conclusion

Pimobendan is a novel agent with properties that are highly desirable in the clinical management of CHF secondary to both DCM and chronic valvular disease in dogs. Review of available data supports that pimobendan is safe, well tolerated, and leads to enhanced quality of life in dogs when used in combination with furosemide or other conventional therapies. Pimobendan reduces mortality in dogs with CHF from DCM, and ongoing studies will better determine its effects on mortality in dogs with chronic valvular disease.

References

1. Cove Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: results of the Cooperative Veterinary Enalapril Study Group. J Vet Intern Med 1995;9:243-252.
2. Ettinger SJ, Benitz AM, Ericsson GF, *et al*. Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. J Am Vet Med Assoc 1998;213:573-577.

3. The BENCH Study Group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. J Vet Cardiol 1999;1:7-18.
4. van Meel JC, Diederen W. Hemodynamic profile of the cardiotonic agent pimobendan. Cardiovasc Pharmacol 1989;14(Suppl 2):S1-S6.
5. Sato N, Asai K, Okumura S, *et al.* Mechanisms of desensitization to a PDE inhibitor (milrinone) in conscious dogs with heart failure. Am J Phys 1999;276:H1699-H1705.
6. Verdouw PD, Hartog JM, Duncker DJ, *et al*. Cardiovascular profile of pimobendan, a benzimidazole-pyridazinone derivative with vasodilating and inotropic properties. Eur J Pharm 1986;126:21-30.
7. Ruegg JC. Effects of new inotropic agents on calcium sensitivity of contractile proteins. Circ 1986;73:78-84.
8. Mathew L, Katz S. Calcium sensitizing agents in heart failure. Drugs Aging 1998;12:191-204.
9. Sasayama S. Immune modulation of cardiac function: a new frontier. J Card Fail 1995;1:331-335.
10. Starling M. Evaluation and management of valvular heart disease. In: Proceed Valves in the Heart of the Big Apple II, New York, 2002, movie presentation.
11. 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;33:1400-1407.
12. Carabello B. Clinical assessment of systolic dysfunction. J Am Coll Cardiol 1994;3:25-29.
13. Urabe Y, Mann DL, Kent RL, *et al.* Cellular and ventricular contractile dysfunction in experimental canine mitral regurgitation. Circ Res 1992;70:131-147.
14. Carabello B, Nolan SP, McGuire LB. Assessment of preoperative left ventricular function in patients with mitral regurgitation: value of the end-systolic wall stress-end-systolic volume ratio. Circulation 1981;64:1212-1217.
15. Carabello B. Mitral valve regurgitation. Curr Prob Cardiol 1998;23:202-241.
16. Fitton A, Brogden RN. Pimobendan. A review of its pharmacology and therapeutic potential in congestive heart failure. Drugs Aging 1994;4:417-441.
17. Durand JB, Bachinski LL, Bieling LC, *et al*. Localization of a gene responsible for familial dilated cardiomyopathy to chromosome 1q32. Circulation 1995;92:3387-3389.
18. O'Grady MR, Minors SL, O'Sullivan L, *et al*. Evaluation of the efficacy of pimobendan to reduce mortality and morbidity in Doberman pinschers with congestive heart failure due to dilated cardiomyopathy (abstract). J Vet Intern Med 2003;17:440.
19. Lombard CW. Clinical experience with pimobendan. In: Proceed Vet Cardio Soc, Brit Small Anim Vet Assoc, Birmingham, 2000.
20. 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;16:255-261.
21. O'Grady MR, Minors SL, O'Sullivan L, *et al.* Evaluation of the efficacy of pimobendan to reduce mortality and morbidity in dogs with congestive heart failure due to chronic mitral valve insufficiency (abstract). J Vet Intern Med 2003;17:410.
22. 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;46:121-130.
23. Haggstrom J, Hamlin R, Hansson K, *et al*. Heart rate variability in relation to severity of mitral regurgitation in Cavalier King Charles spaniels. J Small Anim Pract 1996;37:69-75.