A Double-Blind, Randomized, Placebo-Controlled Study of Pimobendan in Dogs with Dilated Cardiomyopathy

Virginia Luis Fuentes, Brendan Corcoran, Anne French, Karsten E. Schober, Rainer Kleemann, and Claus Justus

A double-blind, randomized, placebo-controlled study was conducted to examine the effect on heart failure class and survival of pimobendan, an oral calcium-sensitizing inodilator, in dogs with dilated cardiomyopathy (DCM). Pimobendan (0.3–0.6 mg/kg body weight/d) or placebo was administered to English Cocker Spaniels (CSs; n = 10) and Doberman Pinschers (DPs; n = 10) that had DCM in addition to background therapy of furosemide, enalapril, and digoxin. Addition of pimobendan to standard triple therapy was associated with a significant improvement in heart failure class, regardless of breed (P < .02, Mann-Whitney rank sum test). Overall, 8 of 10 animals in the pimobendan-treated group, and 1 of 10 animals in the placebo group improved their heart failure status by at least 1 modified New York Heart Association functional class after initial stabilization (P = .005, Fisher’s exact test). Pimobendan had no significant effect on survival in the CSs (P = .77, log-rank test), but DPs treated with pimobendan had significantly longer survival times compared with placebo (P < .02, log-rank test), with a median survival time of 329 days in the pimobendan group compared with 50 days in the placebo group, and a hazard ratio of 3.4 (95% confidence interval 1.4–39.8). Pimobendan resulted in significant improvement in heart failure class when added to standard therapy in this group of dogs with DCM, and may have contributed to improved survival in DPs.

Key words: Calcium-sensitizing agent; Congestive cardiac failure; Doberman Pinscher; English Cocker Spaniel; Heart; Inodilator.

Pimobendan is a benzimidazole-pyridazinone inodilator. Pimobendan causes venodilation and arteriolar dilatation via inhibition of phosphodiesterase (PDE) III, and has positive inotropic effects as a result of both PDE III inhibition (like amrinone and milrinone) and from a calcium-sensitizing effect. Calcium sensitizers affect the interaction of calcium with the troponin C complex, and increase the extent of contraction for a given cytosolic concentration of calcium. The effect of increased preload, whereby increased stretch of the myofilaments results in increased shortening, may operate via a similar mechanism. This inotropic mechanism seems to have advantages, because myocardial energy expenditure is lower than with positive inotropic agents operating via cyclic adenosine monophosphate (cAMP). In skinned myofiber preparations, the rate of adenosine triphosphatase activity per unit force generated is unchanged with addition of pimobendan, despite an increase in active tension. In studies of human patients, additional benefits were seen when pimobendan was added to background therapy of diuretics, ACE inhibitors, and angiotensin-converting enzyme (ACE) inhibitors, and additional benefits were seen when pimobendan was added to background therapy of diuretics, ACE inhibitors, digoxin, and carvedilol.

This double-blind, placebo-controlled trial was undertaken to examine the effects of pimobendan in dogs with naturally occurring dilated cardiomyopathy (DCM). Because differences in the clinical course of DCM have been noted among affected breeds, the interpretation of any response to drug therapy is complex when multiple breeds are involved. Two specific breeds were recruited for this study: Doberman Pinschers (DPs) and English Cocker Spaniels (CSs), reflecting 2 breeds with a contrasting clinical course. DPs have a very poor prognosis, with the majority of dogs surviving less than 6 months after diagnosis. The prog...
nosis is better in CSs, with some dogs surviving for more than 4 years after diagnosis.46,47
The aim of this clinical trial was to evaluate the efficacy and influence of pimobendan on long-term survival in dogs with DCM, when used in combination with background therapy of furosemide, enalapril, and digoxin.

Materials and Methods

The study conformed to the Use of Animals (Scientific Procedures) Act 1986, and informed consent was obtained from each owner.

Subjects

DPs (n = 10) and CSs (n = 10) presented with congestive heart failure resulting from DCM to the Small Animal Clinic, Royal (Dick) School of Veterinary Studies, were recruited for the study. All dogs were currently in modified New York Heart Association (NYHA) class 3 or 4 (Table 1), or had been in modified NYHA class 3 or 4 within the 2 weeks before presentation. Inclusion criteria included echocardiographic confirmation of a dilated, hypococontractile left ventricle in the absence of marked valvular disease or congenital heart defects, and radiographic evidence of pulmonary edema. In 3 of the CSs, subjective thickening of the mitral valve leaflets was noted, but all had an increased left ventricular end-systolic volume index, consistent with myocardial failure.46,47

The gender distribution in the pimobendan and placebo groups was similar, with 1 neutered female in both groups of CSs, and 2 neutered females and 3 males (or neutered males) in each DP group. Median age was 6 years (3–9 years) in the CS placebo group and 9 years (3–14 years) in the pimobendan-treated group. Median age was 10 years (8–10 years) in the DP placebo group and 9 years (6–9 years) in the pimobendan-treated DPs. At the start of therapy, all CSs were in sinus rhythm, and 1 DP in the pimobendan group was in atrial fibrillation, compared with 3 of the placebo-treated DPs. The median NYHA class was 3.0 (3.0–4.0) in the placebo group, and 3.5 (2.0–4.0) in the pimobendan group.

Table 1. Modified New York Heart Association (NYHA) scoring system used to assess functional severity of heart failure.

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Clinical Signs</th>
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<tr>
<td>1</td>
<td>Evidence of cardiac disease, but no clinical signs or exercise intolerance.</td>
</tr>
<tr>
<td>2</td>
<td>Evidence of cardiac disease, but no clinical signs except at exercise. Moderate activity causes fatigue, dyspnea, or both.</td>
</tr>
<tr>
<td>3</td>
<td>Cardiac disease associated with clinical signs such as coughing or dyspnea, but comfortable at rest.</td>
</tr>
<tr>
<td>4</td>
<td>Cardiac disease associated with severe congestive heart failure, such that the animal is exhibiting clinical signs at rest, with little or no capacity for exercise.</td>
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Concurrent Therapy

Prior therapy with diuretics or ACE inhibitors was not an exclusion criterion. On entry to the study, all dogs were treated PO with furosemide, enalapril, and digoxin, and any additional drugs were withdrawn for at least 10 days. Furosemide was given to effect (2–9 mg/kg PO in divided doses), enalapril was given at 0.5 mg/kg PO q12–24h, and serum digoxin concentration was confirmed to be in the therapeutic range of 0.6–1.9 ng/mL before commencement of study drug administration. Mean doses of furosemide, enalapril, and digoxin were not significantly different for placebo- versus pimobendan-treated dogs (Table 2). DPs and CSs were randomized separately to receive either pimobendan (0.3–0.6 mg/kg/d PO) or placebo in addition to standard triple therapy, according to a double-blind protocol. The randomization was carried out off-site in blocks of 10 for each breed, by means of proprietary software, with the identity of the capsules (whether containing pimobendan or placebo) unknown to anyone attending the dogs. No dog received any oral drugs during the study period apart from furosemide, enalapril, digoxin, and either pimobendan or placebo. One CS in the placebo group received topical ear preparations intermittently throughout the study period.

Study Design

The clinical condition of each subject was evaluated at baseline and at 3-week intervals for the DPs, and at 6-week intervals for the CSs. In addition to information on the patient response provided by the owner, a complete physical examination, 6-lead ECG, thoracic radiographs, and echocardiogram were obtained at each reevaluation. The major study variables were modified NYHA class and survival time.

Survival times were calculated as the period from the initiation of pimobendan or placebo treatment until death of the animal, withdrawal from the study, or the end of the 4-year study period (whichever was soonest). Withdrawal from the study was evaluated as a fatality even though survival time may have been longer. Noncardiac causes of death and euthanasia for intractable heart failure were also treated as uncensored data.

Statistical Analysis

Results are reported as the mean ± standard deviation (SD), 95% confidence intervals of the mean (95% CI), or the median value and range. A Fisher’s exact test was used to assess the response to pimobendan or placebo as binary data (improved/not improved) after addition to treatment with conventional therapy. An improvement was indicated by attainment of a lower modified NYHA class at any point during the study period with respect to the NYHA class achieved after stabilization with conventional therapy. For the comparison of survival times, Kaplan-Meier curves were constructed and log-rank tests were used to compare survival curves, with the hazard ratio expressed as 95% CIs. The significance level was set at P < .05. All statistical analyses were carried out with proprietary statistical software programs.

Results

Clinical Efficacy

After initiation of standard triple therapy, both groups improved to a median NYHA class of 2.0 (range in placebo

Table 2. Drug doses at start of trial therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Digoxin (mg/kg/d)</th>
<th>Furosemide (mg/kg/d)</th>
<th>Enalapril (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>English Cocker Spaniel Placebo</td>
<td>0.011 ± 0.002</td>
<td>4.0 ± 2.0</td>
<td>0.62 ± 0.29</td>
</tr>
<tr>
<td>English Cocker Spaniel pimobendan</td>
<td>0.012 ± 0.003</td>
<td>4.0 ± 1.8</td>
<td>0.59 ± 0.23</td>
</tr>
<tr>
<td>Doberman Pinscher placebo</td>
<td>0.008 ± 0.003</td>
<td>5.7 ± 2.4</td>
<td>0.81 ± 0.29</td>
</tr>
<tr>
<td>Doberman Pinscher pimobendan</td>
<td>0.009 ± 0.002</td>
<td>2.9 ± 1.1</td>
<td>0.68 ± 0.27</td>
</tr>
</tbody>
</table>
Pimobendan in Canine DCM

Modified New York Heart Association (NYHA) heart failure class is shown in 10 dogs treated with pimobendan (A) and 10 dogs treated with placebo (B) in addition to treatment with furosemide, enalapril, and digoxin (triple). The graphs show heart failure class on initial presentation, after stabilization with conventional therapy (triple), and then the lowest heart failure class achieved during the study period (triple + pimobendan/triple + placebo). The majority of dogs in both treatment groups improved with conventional therapy, but only 1 of 10 of the dogs in the placebo-treated group showed further improvement after initial stabilization. In the pimobendan group, 8 of 10 dogs showed improvement with the addition of pimobendan to standard therapy (P < .005, Fisher’s exact test).

No statistical difference was found between placebo and pimobendan groups for the NYHA class at initial presentation or after conventional therapy, but a Mann-Whitney rank sum test showed a significant improvement in heart failure class during treatment with pimobendan compared with placebo (P < .02). Only 1 of 10 dogs receiving placebo showed further improvement after stabilization with conventional therapy, whereas 8 of 10 of the dogs receiving pimobendan showed further improvement at some point during the study period (P = .005, Fisher’s exact test).

Two dogs developed diabetes mellitus during the course of the study: a CS in the placebo group, and a DP in the pimobendan group. One CS in the placebo group had 2 episodes of witnessed syncope.

Survival

CSs. Four CSs died during the follow-up period. Three of these animals were euthanized for noncardiac diseases. One dog in the placebo group was euthanized with gastrointestinal disease, and 2 dogs were euthanized in the pimobendan group (1 with a nasal tumor, and 1 with fecal incontinence). One animal in the pimobendan group died suddenly within 1 month of diagnosis. All other CSs were still alive at the end of the study period, although 1 dog from the placebo group was withdrawn from the study with diabetes mellitus. Median survival according to Kaplan-Meier analysis (including all-cause mortality and study withdrawals) was 537 days (range, 61–1,428 days) in the placebo group and 1,037 days (range, 51–1,127 days) in the pimobendan group (P = .77; Fig 2A).

DPs. All DPs died during the study period. Six dogs died suddenly (3 dogs in each group), and 2 dogs were euthanized with intractable cardiac failure (placebo group). One dog in the pimobendan group developed immune-mediated hemolytic anemia that was treated with corticosteroids, and subsequently developed pancreatitis. Signs of congestive failure recurred with fluid therapy, and her death was not observed, so that it was not clear which of the conditions was primarily responsible for her death. The pimobendan-treated DP that developed diabetes mellitus was withdrawn from the study after 329 days. The pimobendan treatment was stopped, although he continued with the standard therapy, and was euthanized for congestive failure 2 months later.

A log-rank test comparing the survival curves showed significant differences between the placebo- and pimobendan-treated DPs (P < .02; Fig 2B). The median survival time for pimobendan-treated DPs was 329 days (range, 42–393 days), and the median survival time in the placebo group was 50 days (range, 13–196 days), with a hazard ratio of 3.4 (95% CI 1.4–39.8).

Discussion

This study examined the effects of pimobendan on dogs with DCM when added to background therapy of furosemide, enalapril, and digoxin. In both breeds, the addition of pimobendan to a standard treatment protocol was associated with a significant improvement in functional heart failure class. Overall, 8 of 10 animals in the pimobendan-treated group improved their modified NYHA-class status during the study period, compared with 1 of 10 animals in the placebo group. Therefore, pimobendan therapy seemed to confer additional benefit over the background therapy of furosemide, enalapril, and digoxin. Although the ages in
No significant difference was found in survival between the placebo- and pimobendan-treated English Cocker Spaniels, with both groups having relatively long survival times. A significant difference was found in the survival curves between the 2 Doberman Pinscher groups, with the pimobendan group having longer survival times ($P < .02$, log-rank test).

At the end of the 4-year study period, 6 of 10 CSs were still alive, and 3 of 10 CSs had died of noncardiac disease, thus confirming previous observations that CSs with DCM have the potential for long survival times. The lack of obvious benefit on survival times does not exclude the possibility of a potential adverse effect of pimobendan in CSs, although the study did not have adequate power to assess this possibility. From the results of this study, any trial undertaking the effect of therapy on the survival of CSs with DCM clearly would have to be of much longer duration and include larger numbers of dogs. Although it had been suspected that survival times might be above average in the CS group compared with historical controls, the magnitude of the survival times and the incidence of noncardiac deaths had not been anticipated.

Although DPs are known to have poor survival times after development of congestive signs, a significant improvement in survival was found for pimobendan-treated animals, with a median survival of 50 days in the placebo group compared with 329 days in the pimobendan group ($P < .02$, log-rank test).

This finding contrasts with the prevailing attitude to use of positive inotropic agents in the treatment of chronic heart failure in human patients, where a number of trials have revealed adverse effects on survival despite short-term hemodynamic benefits. Even where short-term quality of life is markedly improved, any increase in mortality is considered unacceptable in the treatment of human heart failure. However, the appropriate use of positive inotropic agents in human patients is an area of controversy, especially because differences may occur in outcome according to dose and whether treatment is short-term, intermittent, or long-term. The cause of the increased mortality seen with long-term use of some positive inotropes in human patients is unknown, but may be related to increased cytosolic calcium concentrations, because increased calcium concentrations predispose to arrhythmia, and may increase the likelihood of sudden death. Additional problems associated with positive inotropes include increased myocardial energy expenditure, although this is less true of PDE inhibitors, where the arteriodilating effects may reduce myocardial workload sufficiently to offset increased energy consumption from increased contractility.

Pimobendan was shown to increase survival in cardiomyopathic Syrian hamsters, although patients have shown reduced numbers of hospitalizations or adverse events with pimobendan compared with placebo, although no studies have been published of human heart failure patients where survival has been a primary endpoint. A number of studies that used 24-hour Holter monitoring failed to demonstrate any proarrhythmic tendencies. The Pimobendan in Congestive Heart Failure (PICO) trial of 317 patients followed over 6 months was not designed as a survival study, but showed a nonsignificant trend toward increased mortality in the low-dose group of pimobendan-treated patients. However, the number of sudden cardiac deaths in the high-dose pimobendan group of the PICO study was identical to that of the placebo group. In a recent study of patients with nonischemic DCM who were unable to tolerate beta-adrenergic antagonists, pimobendan had no adverse effect on survival over 2 years when added to standard therapy. In this human study, patients treated with pimobendan in addition to standard therapy had lower requirements for additional medications for worsening heart failure, compared with patients receiving standard therapy and placebo. Differences may occur in outcome between cardiomyopathic patients of ischemic and nonischemic origin, with a more favorable response to pimobendan in the latter. Nevertheless, in the absence of any specifically designed survival trials, whether the effect of pimobendan on mortality in human heart failure patients differs from that of other positive inotropic agents is unclear.

The addition of pimobendan to conventional therapy in DPs in our study resulted in a survival advantage, although
the true magnitude of the effect is difficult to assess with the uneven number of dogs with atrial fibrillation in the 2 groups. The effect on survival in CSs was unclear, because their survival times in general were so long. The possibility of a contributory effect to the sudden death of the CS in the pimobendan group cannot be ruled out, although no trend was found toward increased sudden death in the DPs. The effect of positive inotropic agents on survival in dogs with naturally occurring heart failure has not been critically evaluated, and the validity of extrapolating from human survival trials remains unknown. Despite ominous long-term effects in human heart failure patients with ischemic disease, clinical trials of milrinone appeared very promising in the treatment of heart failure in dogs, although the studies were never extended to long-term, placebo-controlled trials.

Factors possibly were operating that may have adversely influenced survival in the DP placebo group, contributing to the differences in survival. The DP placebo group included an increased number of dogs with atrial fibrillation (3 of 5 dogs, versus 1 of 5 dogs in the pimobendan group). Atrial fibrillation has been shown to be associated with poor survival times in DPs with DCM, with a median survival time of only 2.9 weeks in 1 study. In view of this, it would have been preferable to have a separate randomization schedule for dogs with atrial fibrillation, because the survival times would be expected to be shorter. The randomization unfortunately resulted in an uneven distribution of atrial fibrillation cases, which may have unduly affected the outcome. The trend toward a higher furosemide dose in the DP placebo group may reflect this. However, the sample size was too small to allow a subanalysis of the DPs without the atrial fibrillation cases. Nevertheless, the dog with atrial fibrillation in the pimobendan group survived for 265 days, despite having ascites and pleural effusion on initial presentation. The combination of atrial fibrillation and biventricular failure was associated with a particularly poor prognosis in the study by Calvert et al., with such dogs having a median survival time of only 2.0 weeks and a range of <1–13 weeks, yet this DP survived for 37 weeks. With only 1 DP with atrial fibrillation in the pimobendan group, knowing if this was a chance effect or related to the pimobendan treatment is difficult. One of the pimobendan-treated DPs subsequently developed atrial fibrillation after being withdrawn from the study (and thus withdrawn from pimobendan treatment, although continuing with standard treatment) and 1 of the placebo-treated CSs developed atrial fibrillation during the course of treatment.

Although some of the benefit seen in the pimobendan-treated DP most likely was associated with sustained improvement in hemodynamic function, other factors also may have played a role. By improving hemodynamic function, pimobendan may have resulted in an indirect reduction in neurohormonal activation. Several studies have shown a reduction in neurohormonal activation, with reductions in plasma norepinephrine levels, atrial and brain natriuretic hormones, and endothelin-1 levels. Also, effects are apparent on proinflammatory cytokines, with reductions reported in tumor necrosis factor α and interleukin (IL)-1β and IL-6.

Whenever euthanized animals are not censored in survival studies, the influence of timing of euthanasia must be considered. Two of the placebo-treated DPs were euthanized at the request of the owners after developing intrac table congestive cardiac failure that did not respond to increasing the dosage of diuretics. Two of the pimobendan-treated dogs also developed congestive heart failure during the study period, but this was after developing anemia and pancreatitis in 1 dog, and after withdrawal of pimobendan after development of diabetes mellitus in the other. The latter dog’s survival time was assessed up to the point of withdrawal from the study, although he survived a further 2 months on standard triple therapy without pimobendan before developing a recurrence of congestive signs. In both cases, development of congestive heart failure was more than 350 days after entering the study.

No attempt was made to record 24-hour ambulatory ECGs, or to stratify the risk of fatal arrhythmia. Three sudden deaths occurred in each DP treatment group, and 1 sudden death occurred in the pimobendan-treated CS group, all of which were assumed to be cardiac. Although adverse effects on survival were not apparent in this study, ambulatory ECG recordings would be important in identifying the risk of proarrhythmia associated with pimobendan, and should be considered in a larger study.

Diet was not standardized during the study, although supplementation with taurine and carnitine has been shown to be helpful in American Cocker Spaniels with DCM. Serum or whole blood taurine concentrations were not measured in any of the dogs in this study, although the authors have previously failed to identify low serum taurine concentrations in any CSs with DCM (unpublished observations).

Blood pressure was not routinely recorded during this study, although hypotension is a potential risk with severe DCM, use of ACE inhibitors, and with the vasodilating effects of pimobendan. Hypotension, if present, did not appear to result in clinical signs.

Although the sample size in this study was small, the results suggest that pimobendan may be a useful treatment for dogs with congestive heart failure associated with DCM. Pimobendan resulted in improvement in functional heart failure class, and was associated with reduced mortality in the DPs presenting with congestive heart failure in this study. These results suggest that undertaking a larger study with a longer duration of follow-up would be worthwhile, to evaluate the effect of pimobendan in a broader range of dogs with DCM.

Footnotes

1 Enalapril Cardiovet, Intervet Ltd, Milton Keynes, Bucks, UK
2 Lanoxin, Greenford, Middlesex, UK
3 SAS, SAS Institute Inc, Cary, NC, USA
4 SigmaStat 2.0, Jandel Scientific, San Rafael, CA, USA
5 Prism, Version 3.0, GraphPad Software, Inc, San Diego, CA, USA

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