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Milrinone

A Clinical Trial in 29 Dogs With Moderate to Severe Congestive Heart Failure

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Milrinone, a positive inotropic drug with vasodilating properties, was administered at doses of 0.5 to 1 mg/kg orally twice daily to 29 dogs with moderate to severe congestive heart failure (CHF). Significant echocardiographic improvement in ventricular systolic function was observed after 3 days of administration of milrinone and at the patients' last echocardiographic observation (day 21 in 25 subjects, day 7 in 2 subjects, and day 3 in 2 subjects). Echocardiographic shortening fraction at the initial measurement had a median increase of 6.14% \((P < 0.001)\), and for the last observation a 2.83% increase \((P < 0.005)\). Most patients also showed improvement in their clinical signs as assessed by the veterinarian (72%) and by owner’s evaluation (81%). No consistent problem or adverse reaction to milrinone was observed, except for a small number of clinically manageable ventricular dysrhythmias. Milrinone appears in this trial to be effective for the treatment of advanced CHF in dogs. (Journal of Veterinary Internal Medicine 1990; 4:79-86)

MILRINONE is an inotropic and vasodilating agent undergoing clinical investigation in both humans and dogs.\(^1\)\(^-\)\(^13\) The drug is a bipyridine compound, similar in structure to amrinone, but with chemical modifications that have improved potency. Like amrinone, the drug is nonglycoside and noncatecholamine agent.

The possible mechanisms of action have been studied both \textit{in vitro} and \textit{in vivo}. There is evidence that milrinone causes an increase in cardiac cyclic-AMP concentrations and that part of this increase may be explained by phosphodiesterase inhibition; however, whether this is responsible for the inotropic/vasodilator activity of the drug has not been fully established.\(^14\)\(^-\)\(^17\) In addition, milrinone may increase cyclic-AMP, and therefore contractility, by inhibiting the inhibitory regulator subunit \(N\)i, on the beta receptor. Covalent modification of this inhibitory regulator by pertussis intoxication abolishes inotropic-mediated stimulation on adenyl cyclase activity. Milrinone also is a competitive antagonist of \(A_1\) adenosine receptors, which may result in an increase in inotropy.\(^18\)

The inotropic and chronotropic activity of milrinone has been documented in \textit{ex vivo} systems including isolated cat, rabbit, and guinea pig right atria and papillary muscles.\(^19\)\(^,\)\(^20\) \textit{In vivo} studies have included anesthetized dogs, conscious dogs, and acute, drug-induced and non-drug-induced models of heart failure in anesthetized dogs.\(^21\)\(^,\)\(^22\)\(^,\)\(^23\) To date, this and other bipyridine compounds have also been studied in the pig, sheep, and horse.\(^24\)\(^,\)\(^25\)\(^,\)\(^26\) Clinically, milrinone has been studied in dogs with naturally occurring congestive heart failure (CHF) under several different investigational protocols.\(^8\)

The proposed clinical use in dogs is the treatment of CHF, in which left or right ventricular myocardial function is inadequate. This myocardial dysfunction could be due to several abnormalities, including dilated cardiomyopathy, valvular dysfunction (acquired and congenital), or heartworm disease.
Milrinone's dose (0.5–1 mg/kg twice daily), and acute and chronic efficacy have been established in dogs with naturally occurring myocardial failure and minimal clinical signs. An ancillary study confirmed that a twice-daily regimen was adequate to sustain ventricular function. Although milrinone used alone was sufficient to treat CHF in these studies, the practical clinical use of milrinone is projected to be in combination with other cardiovascular drugs.

This study was initiated in order to determine the efficacy of milrinone in dogs with CHF receiving conventional cardiovascular drugs, e.g., digitalis, furosemide, and to determine obvious adverse reactions associated with this drug. All patients in this study received milrinone in combination with another cardiovascular drug at some point during the study period. Before initiation of the milrinone, CHF was being managed by nonpharmacologic means, i.e., exercise restriction and salt-restricted diet, in only three patients.

The objectives of this study were 1) to determine whether adding milrinone to preexisting therapeutic regimens was well tolerated and apparently safe, as determined by monitoring adverse reactions; 2) to determine whether echocardiographic indices of ventricular function would improve over baseline when milrinone was added to preexisting therapeutic regimens; and 3) to determine whether clinical signs improved when milrinone was added to preexisting therapeutic regimens in dogs showing signs of CHF.

Materials and Methods

This study was preceded by a double-blind, placebo controlled study that employed a withdrawal phase design. After that experience, most of the investigators expressed some reservation regarding any further placebo controlled trials. The problem with placebo controlled trials is that prospective stratification is often required, since randomization of a CHF population with small sample sizes tends to result in unequal groups. A prospective stratification design generally requires large sample sizes. This trial was one of four studies involving a total of 368 cases. Baseline (predrug) studies were conducted on all patients. These baseline data served as the basis of comparison with all views of data at the assigned intervals throughout the rest of the study. Intensive examinations of the patients were conducted by observing clinical signs and echocardiography for 21 days after initiating milrinone administration and then clinical signs only through 81 days. Patients surviving beyond that time remained on milrinone but were examined less intensively and less frequently.

Objective data reported here were viewed early in the study (at day 3 “initial response” and up through day 21) when the bias of natural degeneration of the diseased heart was reduced. Long-term efficacy was assessed by subjectively evaluating the patients at the completion of the study (day 81) or at their last observation before death. Clinical efficacy was evaluated by examining the veterinarian’s and the owner’s assessment of the type and severity of the clinical signs. The last echocardiographic observation was at day 21 or at the last observation before death. Viewing data in this way (last observation) reduces the bias of removing nonresponders that died earlier in the study. Thus, a last observation analysis uses a more conservative approach since it includes both responders and nonresponders.

Study Population

Twenty-nine dogs were selected for this study. The breed, sex, age, weight, estimated body surface area, and primary diagnosis of each patient are shown in Table 1. Patients were predominantly working-class breeds; however, a variety of breeds was represented. Age ranged from four months to 13 years with a mean ± standard deviation (SD) of 6.51 ± 3.30 years. Weight ranged from 7.7 to 67.2 kg with a mean ± SD of 32.44 ± 12.88 kg. Body surface area ranged from 0.39 to 2.06 with a mean ± SD of 1.04 ± 0.32 m².

Compared with the previous trial, patients tended to have a wider variety of underlying cardiac diseases, tended to be more severely decompensated, and were generally failing on conventional medication, e.g., digitalis, glycosides, and diuretics.

Nineteen patients were diagnosed as having dilated cardiomyopathy. Of these 19, nine had secondary valvular regurgitation. Three patients had primary valvular disease. Six patients had occult or overt heartworm disease. One patient had doxorubicin*-induced myocardial failure.

Echocardiography

Routine echocardiograms were taken at baseline and were repeated at approximately three, seven, 14, and 21 days after beginning milrinone therapy. Echocardiographic parameters were used to assess ventricular function and included shortening fraction (SF) [SF was defined as left ventricular SF for patients with primarily left ventricular failure LV and right ventricular SF for patients with primarily right ventricular RV failure]. Left ventricular shortening fraction (LVSF) and left ventricular ejection fraction (LVEF) were calculated using the method of Teichholz.† Right ventricular shortening fraction (RVSF) and mean velocity of circumferential fiber shortening (mean Vcf) was calculated using the left ventricular ejection time (LVET) as measured from the onset of the opening to the closing of the aortic valve.

* Adriamycin*, Adria Laboratories, Dublin, OH.
† LVEF by this method has not been validated for the dilated ventricle and is presented here for completeness only.
Vol. 4  Number  Breed  Sex  Neutered (kg) (M2) (yrs)  Primary Diagnosis
1  Afghan Hound  M  I  21.8  0.78  9.0  Dilated cardiomyopathy
2  Doberman  M  I  39.0  1.15  8.5  Dilated cardiomyopathy
3  Doberman  M  I  33.1  1.03  6.0  Dilated cardiomyopathy
4  Cairn Terrier  M  N  7.7  0.39  13.0  Valvular heart disease endocardiosis (mitral and tricuspid)

(Five consecutive beats were average in cases of atrial fibrillation). Other echocardiographic measurements were made, including systolic time intervals (prejection period and left ventricular ejection time). Heart rates (HR) were measured by analyzing an ECG.

**Physical Examination/Clinical Signs**

Physical examinations were performed on all patients. Heart rate and respiratory rates were measured periodically. The amount or degree of orthopnea, dyspnea, edema, and fatigue were subjectively ranked by the attending veterinarian and subsequently scored (Table 2). Patients also were subsequently ranked from this assessment as to the severity of prognostic class of their heart failure and categorized as “slightly compromised,” “moderately compromised,” or “severely compromised.” If the sign was “bad” or “very bad,” the patient’s condition was ranked as “severely compromised”; if “moderate” was the worst score, the rank was “moderately compromised”; if “slight” or “no problem,” the rank was “slightly compromised.” “Slightly,” “moderately,” and “severely compromised” are terms originally devised by the New York Heart Association and are similar to New York Heart Association Functional Class II, III, and IV, respectively.27

<table>
<thead>
<tr>
<th>Number</th>
<th>Breed</th>
<th>Sex</th>
<th>Neutered</th>
<th>Weight (kg)</th>
<th>BSA (M2)</th>
<th>Age (yrs)</th>
<th>Primary Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Afghan Hound</td>
<td>M</td>
<td>I</td>
<td>21.8</td>
<td>0.78</td>
<td>9.0</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>2</td>
<td>Doberman</td>
<td>M</td>
<td>I</td>
<td>39.0</td>
<td>1.15</td>
<td>8.5</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>3</td>
<td>Doberman</td>
<td>M</td>
<td>I</td>
<td>33.1</td>
<td>1.03</td>
<td>6.0</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>4</td>
<td>Cairn Terrier</td>
<td>M</td>
<td>N</td>
<td>7.7</td>
<td>0.39</td>
<td>13.0</td>
<td>Valvular heart disease endocardiosis (mitral and tricuspid)</td>
</tr>
</tbody>
</table>

M: male; F: female; BSA: body surface area.
Owner Evaluation

Owners were questioned as to their perception of the disease status. The primary questions involved the patient’s ability to function as a household pet with reasonable quality of life with regard to exercise, coughing, breathing, fainting, and appetite. Questionnaires for the owners were designed to quantify a change in home behavior. Questions were asked regarding the quantity and vigor of exercise, the frequency of coughing and relationship of coughing to rest and exercise, frequency of fainting, incidence of labored breathing, and an assessment of the patient’s appetite. Each of the five questioned areas were graded from 0 to 3 (0 = worst case, 3 = best case) such that an overall score of 0 was the most severe and 15 would be essentially a normal patient.

Laboratory Parameters

Full laboratory analyses, including serum enzymes, electrolytes, complete urinalysis, fecal flotation and occult blood, and dirofilaria screens, were performed and examined for changes from predrug to seven days after starting milrinone administration.

Other Clinical Assessments

Electrocardiograms (ECG) and radiographs of the thorax and abdomen were assessed before starting milrinone administration and at approximately three, seven, 14, and 21 days after the initiation of milrinone therapy.

Drug Administration

All patients received milrinone as an oral liquid formulated in concentrations of 1, 5, or 10 mg/ml, and administered at 0.5 to 1.0 mg/kg twice daily starting after baseline measurements were accumulated.

Statistical Methods

For echocardiographic data, the hypothesis of no change from baseline was tested using a nonparametric Signed Rank Test. One-way analysis of variance was also done with similar results. Wilcoxon Signed-Rank Test is used in this case because it accounts for variable baseline data and represents a more conservative analysis. The null hypothesis was rejected if the P value was less than 0.05. Subjective assessments of drug response proportion (clinical signs and owner’s evaluations) are expressed with 95% confidence intervals.

Results

Echocardiography

Baseline echocardiograms showed 17 patients with severe myocardial failure (LVSF < 20%), six with moderate myocardial failure (LVSF = 20–25%), and two with slight myocardial failure (LVSF = 26–30%).

LVSF ranged from 7.46 to 51.35%. RVSF ranged from 16.67 to 26.47%. LVEF ranged from 16.15 to 83.27% and mean V_e ranging from 0.49 circ/sec to 3.31 circ/sec. Heart rate ranged from 81 to 220 beats/min.

Shortening fraction, LVSF, RVSF, LVEF, and V_e increased significantly after three days of treatment and/or at the last observation (Table 3). Echocardiographic values improved in the majority of the patients (Figs. 1 to 4). Systolic time interval measurements did not change significantly.

Right ventricular function improved in all patients with either occult or overt heartworm disease and severe congestive heart failure.

Physical Examinations/Clinical Signs

Vital signs generally improved. Heart rate by auscultation was reduced with a median change of −30 beats/min by day 81. Body temperature changes were not significant except in patients with concurrent infection.

Signs initially improved in the majority of patients with further improvement by day 7. Improvements tended to persist through day 81 in surviving patients (16 of 20). At the patients’ last observations, 72% had improved clinical signs (95% Confidence Interval, 53–87%). One patient’s clinical signs had not changed and seven patients’ clinical signs had declined. The mean score for the entire group improved from 4.4 to 5.0 at the last observation (Table 4).

<table>
<thead>
<tr>
<th>TABLE 3. Echocardiographic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong> Baseline</td>
</tr>
<tr>
<td>Shortening Fraction</td>
</tr>
<tr>
<td>LV Shortening Fraction</td>
</tr>
<tr>
<td>RV Shortening Fraction</td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
</tr>
<tr>
<td>Mean V_e Circumferential Fiber Shortening</td>
</tr>
<tr>
<td>Heart Rate by ECG</td>
</tr>
</tbody>
</table>

NS: not significant.

* P value for signed-rank test of change from baseline.

† Last observation ≤ Day 21.
Figs. 1 to 4. Echocardiographic data for each individual dog at evaluated time points for left ventricular shortening fraction, left ventricular ejection fraction, right ventricular shortening fraction, and mean circumferential fiber shortening.

Fig. 1.

**LEFT VENTRICULAR SHORTENING FRACTION**

**RIGHT VENTRICULAR SHORTENING FRACTION**

**LEFT VENTRICULAR EJECTION FRACTION**

**MEAN CIRCUMFERENTIAL FIBER SHORTENING**

**FIG. 1.**

**FIG. 2.**

**FIG. 3.**

**FIG. 4.**
Patients improved in class of failure at day 3 and the last observation (Tables 5 and 6). The majority of patients (68%) in the "severely compromised" or "moderately compromised" class improved up through their last observation.

No extraordinary changes in physical condition occurred with the addition of milrinone except those changes associated with the relief of signs of CHF. Milrinone had no apparent deleterious effects on any of the major body systems.

Owner Evaluation

Owners perceived overall improvement in 81% (95% Confidence Interval, 61–93%) of the patients at their last observation. The average score improved from 7.6 to 10.6 (Table 4). Most of the patients' improvements occurred in exercise tolerance and appetite. These improvements generally correlated with improvements observed in clinical signs. Frequently, owners stated that their pets had improved remarkably.

Other Clinical Assessments

Aside from detecting occasional ventricular arrhythmias described in adverse reaction section below, ECGs failed to detect any changes. Radiographs showed decreasing lung densities in most cases, but did not reliably detect heart size reductions.

Laboratory Parameters

No consistent trends were seen in day 7 laboratory parameters. Milrinone apparently did not enhance the side effects of conventional therapies nor did the other drugs enhance any unanticipated side effects of milrinone. There were no significant changes in liver enzymes, blood parameters, or urinalyses.

Drug Schedule/Concomitant Medications

The average initial dose of milrinone was 0.535 mg/kg administered twice daily. During the course of the study, milrinone dosage was increased in 65% of the patients with the mean mg/kg twice-daily dose being 0.763 by the last reported day of milrinone administration. In two patients milrinone was administered on a three-times-daily schedule later in the study.

No clinically significant changes in concomitant medication usage occurred. The mean mg/dog/day dose of concomitant medications and number of patients receiving those concomitant medications remained stable through the study.

Adverse Drug Reactions

Only three patients experienced adverse reactions that, in the opinion of the investigator, were definitely associated with milrinone. These were ventricular arrhythmias and were ranked as “serious” or “moderate.” One patient died; however, this patient had a documented ventricular tachycardia after the first dose of milrinone and died after the second dose, having never received antiarrhythmic therapy. One patient was removed from milrinone and recovered. The third patient was treated with procaainamide and the arrhythmia resolved.

During milrinone administration, adverse reactions

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### Table 4. Efficacy Parameters Baseline Versus Last Observation*

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>%†</th>
<th>95% CI</th>
<th>No.</th>
<th>%†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>21</td>
<td>72</td>
<td>(53, 87)</td>
<td>21</td>
<td>81</td>
<td>(61, 93)</td>
</tr>
<tr>
<td>No change</td>
<td>1</td>
<td>4</td>
<td></td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Declined</td>
<td>7</td>
<td>24</td>
<td></td>
<td>4</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>—</td>
<td>—</td>
<td></td>
<td>3</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline** | **Last Observation**

| Mean Score | 4.4 | 5.0 | 7.6 | 10.6 |

Cl: confidence interval.
* Last observation.
† % Total observed.

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### Table 5. Clinical SignsBaseline versus Initial Response (day 3)

<table>
<thead>
<tr>
<th>Classification Pretreatment</th>
<th>Severely Compromised</th>
<th>Moderately Compromised</th>
<th>Slightly Compromised</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe compromised (n) (%)</td>
<td>8 (28.6)</td>
<td>4 (14.3)</td>
<td>3 (10.7)</td>
<td>15 (53.6)</td>
</tr>
<tr>
<td>Moderate compromised (n) (%)</td>
<td>1 (3.6)</td>
<td>3 (10.7)</td>
<td>5 (17.9)</td>
<td>9 (13.1)</td>
</tr>
<tr>
<td>Slightly compromised (n) (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Total (n)</td>
<td>9 (32.1)</td>
<td>7 (25.0)</td>
<td>12 (42.9)</td>
<td>28 (100.0)</td>
</tr>
</tbody>
</table>
of "uncertain" or "no" association with milrinone included mild anorexia with no sequelae, possible acute nephritis as evidenced by hyaline casts in the urine with recovery while still on drug treatment, moderate nephritis with recovery, severe atrial fibrillation with no sequelae, moderate nausea and vomiting, moderate diarrhea in one patient, and moderate vomiting and diarrhea in another, both recovering (while drug continued).

Deaths occurred in eight patients before day 81. Death in all but the one patient was attributed to progression of the heart disease or concurrent disease.

Survival
As of 6/85, two patients in the study were alive. These two, heartworm patients, were considered to be cured of their CHF and heartworm disease and were no longer receiving milrinone. The last patient on milrinone to die in this study did so after 2.25 years on milrinone.

Survival curves on patients in this study are shown in Figure 5. Approximately 20% of the patients survived 400 days. No historic data has been published on the survivability of a broad base of canine CHF patients and so no comparison can be made.

Discussion
The objectives of this study were to examine the safety of using milrinone in patients receiving other cardiovascular drugs and to determine the efficacy of milrinone by evaluating the echocardiographic response to its administration and evaluating the clinical response of the animal.

In this group of 29 dogs, adverse reactions, which an investigator was certain were due to milrinone administration, were uncommon and consisted only of ventricular arrhythmias. In two of the three dogs the arrhythmia was controlled by either removing the dog from the drug or by treating the arrhythmia with an antiarrhythmic agent. In one dog a ventricular tachycardia was identified but the drug administration was not discontinued and an antiarrhythmic agent was not administered and the patient died following the second dose of the drug. Therefore it is recommended that dogs that are prone to arrhythmia, e.g., cardiomyopathy, that receive milrinone be monitored with an electrocardiogram at some time between 1 hour and 2.5 hours after the first dose. If an arrhythmia is identified, milrinone should either be discontinued or an antiarrhythmic drug administered. If the arrhythmia cannot be controlled with drugs, milrinone administration should be stopped.

Adverse effects other than the arrhythmias were either mild or probably unrelated to milrinone administration. Of the problems noted during milrinone therapy that were classified as severe and as having an uncertain relationship to milrinone administration, both resolved while the dogs were still receiving milrinone. Of adverse reactions classified as moderate, and having uncertain or no relationship to milrinone, all were related to gastrointestinal distress and three of the four dogs recovered while milrinone administration continued. Since these patients suffered from CHF and were on concomitant medications, it was difficult for the investigator to evaluate adverse reactions that were due to milrinone. No abnormalities in blood counts or serum chemistries

<table>
<thead>
<tr>
<th>Classification Pretreatment</th>
<th>Severely Compromised n (%)</th>
<th>Moderately Compromised n (%)</th>
<th>Slightly Compromised n (%)</th>
<th>Totals n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe compromised</td>
<td>1 (3.4)</td>
<td>8 (27.6)</td>
<td>6 (20.7)</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Moderately compromised</td>
<td>4 (13.8)</td>
<td>3 (10.3)</td>
<td>3 (10.3)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Slightly compromised</td>
<td>0 (0.0)</td>
<td>2 (6.8)</td>
<td>2 (6.8)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Total n (%)</td>
<td>5 (17.2)</td>
<td>13 (44.8)</td>
<td>11 (37.9)</td>
<td>29 (100.0)</td>
</tr>
</tbody>
</table>
were noted in any dog receiving milrinone. Until additional studies are fully considered, a statement as to the safety of using milrinone in dogs with heart failure cannot be made definitively. However, milrinone appeared to be safe in the present group of dogs as long as appropriate monitoring was performed.

As noted in previous studies, milrinone in the present study was efficacious in that it improved echocardiographic measures of cardiac function. The present study, in contrast to previous studies, also documented that the improvement in cardiac function translated into improved clinical signs. One must be careful in this interpretation since both observers (the dog owner and the veterinarian) knew that each dog was receiving milrinone. In other words, there was no placebo control in this study and neither the owner nor the veterinarian were blinded to the fact that milrinone was being administered. Therefore, each observer was either biased negatively or positively. However, it is the opinion of the authors that milrinone did in fact improve clinical signs and in some dogs did so dramatically. In 72% of the cases the veterinarian felt that the dog being treated improved clinically. In 81% of the patients, owners perceived improved quality of life while observing the patient in its home setting. These responses were noted while the doses of other cardiovascular drugs remained stable, indicating that clinical and echocardiographic responses were most likely the result of milrinone therapy.

References


20. Sys SU, Brutsaert DL. No tachyphylaxis observed following chronic pretreatment with amrinone or milrinone in mammalian cardiac muscle (Abstr). European Heart Journal 1984; (Suppl I):50.


