Effects of long-term administration of enalapril on clinical indicators of renal function in dogs with compensated mitral regurgitation

Clarke E. Atkins, DVM, DACVIM; William A. Brown, DVM, DACVIM; Julie R. Coats; Mary Ann Crawford, DVM, DACVIM; Teresa C. DeFrancesco, DVM, DACVIM; Julie R. Coats; Philip R. Fox, DVM, DACVIM; Bruce W. Keene, DVM, MS, DACVIM; Linda Lehmkuhl, DVM, DACVIM; Michael Luethy, DVM, DACVIM; Kate Meurs, DVM, PhD, DACVIM; Jean-Paul Petrie, DVM, DACVIM; Frank Pipers, DVM, PhD; Steven Rosenthal, DVM, DACVIM; Jennifer A. Sidley, DVM, DACVIM; Justin Straus, DVM, DACVIM

Objective—To determine the effect of long-term administration of enalapril on renal function in dogs with severe, compensated mitral regurgitation.

Design—Randomized controlled trial.

Animals—139 dogs with mitral regurgitation but without overt signs of heart failure.

Procedure—Dogs were randomly assigned to be treated with enalapril (0.5 mg/kg [0.23 mg/lb], PO, q 24 h) or placebo, and serum creatinine and urea nitrogen concentrations were measured at regular intervals for up to 26 months.

Results—Adequate information on renal function was obtained from 132 dogs; follow-up time ranged from 0.5 to 26 months (median, 12 months). Mean serum creatinine and urea nitrogen concentrations were not significantly different between dogs receiving enalapril and dogs receiving the placebo at any time, nor were concentrations significantly different from baseline concentrations. Proportions of dogs that developed azotemia or that had a ≥35% increase in serum creatinine or urea nitrogen concentration were also not significantly different between groups.

Conclusions and Clinical Relevance—Results suggest that administration of enalapril for up to 2 years did not have any demonstrable adverse effects on renal function in dogs with severe, compensated mitral regurgitation. (J Am Vet Med Assoc 2002;221:654–658)

Angiotensin-converting-enzyme (ACE) inhibitors have been found to be useful in the management of hypertension and heart failure in humans1–3 and heart failure in dogs.4–9 Although the overall safety record during short-term use has been good, there are concerns as to the adverse effects of ACE inhibitors on renal function.10–13 Because of the widespread use of ACE inhibitors in dogs with heart failure and because of the potential for long-term use in dogs with systemic hypertension or cardiac disease that do not yet have overt signs of heart failure, information on the effects of long-term use of ACE inhibitors on renal function in dogs is needed. The purpose of the study reported here was to determine whether long-term enalapril administration would have any adverse effects on renal function in dogs with severe, compensated mitral regurgitation. The study was conducted as part of an ongoing long-term randomized controlled trial of the efficacy of enalapril in the treatment of dogs with naturally occurring mitral regurgitation but mild or no signs of heart failure.

Materials and Methods

Patient selection—Dogs included in the present study were client-owned animals that had been enrolled in an ongoing multicenter randomized controlled trial of the efficacy of enalapril in dogs with heart disease. Specifically, this trial was designed to determine whether initiating treatment with enalapril prior to the onset of congestive heart failure in dogs with New York Heart Association class-I or -II heart disease would delay the onset of pulmonary edema. Board-certified cardiologists and internists at 8 university-based veterinary teaching hospitals and private referral practices enrolled dogs in the study. Dogs were eligible for inclusion in the study if the were >5 years old, weighed <20 kg (44 lb), had echocardiographic evidence of mitral valve endocardiosis and insufficiency and left atrial enlargement (left atrial-to-

From the Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Atkins, Coats, DeFrancesco, Keene, Sidley); Veterinary Cardiology Consults, 1886 Birmingham Blvd, Birmingham, MI 48009 (Brown); Oradell Animal Hospital, 481 Kinderkamack Rd, Oradell, NJ 07649 (Crawford, Straus); Albany County Veterinary Hospital, 148 Bozekill Rd, Albany, NY 12203 (Edwards); The Animal Medical Center, 510 E 62nd St, New York, NY 10021 (Fox, Petrie); the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210 (Lehmkuhl, Meurs); Cardioscope Pet Referral Service, 1820 Frontage Rd, Northbrook, IL 60062 (Luethy); Merial Inc, 3239 Satellite Blvd, Duluth, GA 30096 (Pipers); and Chesapeake Veterinary Referral Center, 808 Bathgate Rd, Annapolis, MD 21401 (Rosenthal). Dr. Lehmkuhl’s present address is MedVet Specialty Clinic, 5747 Cleveland Ave, Columbus, OH 43213. Dr. Straus’ present address is Animal Emergency and Referral Center, 647 Bloomfield Ave, West Caldwell, NJ 07006. Dr. Sidley’s present address is Chesapeake Veterinary Referral Center, 808 Bathgate Rd, Annapolis, MD 21401. Dr. Pipers’ present address is Dove Lewis Emergency Animal Hospital, 1984 NW Petrygove Ave, Portland, OR 97209.

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Address correspondence to Dr. Atkins.
aortic diameter ratio > 1.6 on an M-mode or 2-dimensional short axis view), and had radiographic evidence of cardiomegaly. Dogs with systemic hypertension, radiographic evidence of pulmonary edema, or concurrent disease processes that, in the opinion of the investigator, would result in death in < 1 year were excluded. Owners of dogs included in the study provided informed consent.

Dogs enrolled in the enalapril efficacy trial were eligible for inclusion in the present study if serum creatinine and urea nitrogen concentrations had been measured before and at least once after initiation of treatment with enalapril. Serum creatinine and urea nitrogen concentrations were measured, using validated procedures, at the participating institutions or by private commercial laboratories.

Treatment and monitoring—For all dogs, a complete physical examination, echocardiographic and thoracic radiographic examinations, and laboratory evaluations (CBC, urinalysis, and serum biochemical profile) were performed at the time of enrollment in the study. Dogs were then randomly assigned to be treated with enalapril (0.3 mg/kg [0.23 mg/lb], PO, q 24 h) or a placebo. Owner compliance was determined by a combination of owner interrogation, examination of daily pill administration logs, and pill counts; dogs were removed from the study if owner compliance was inadequate. Serum urea nitrogen and creatinine concentration were measured at the time of enrollment in the study; approximately 0.5, 3, 6, 9, 12, 15, and 18 months later; and approximately every 4 months thereafter, as needed. In addition, if signs compatible with heart failure (cough or dyspnea) were detected during a routine follow-up examination or were reported by the owner, the dog was reevaluated and thoracic radiographs obtained. Once congestive heart failure, defined as radiographic evidence of pulmonary edema, developed, the group assignment code was broken, and the dog was treated as deemed necessary by the attending clinician. Group assignment (enalapril or placebo) of each dog enrolled in the study was known by only 1 person (JRC), the lead technician in the study, who played no role in clinical decision-making.

Statistical analyses—The integrity of the primary study was the highest priority; therefore, interim analyses were performed with great care to avoid disclosure of the status of individual dogs. Interim analyses of renal safety at approximately 12 and 24 months and final analysis at 38 months were performed by identifying dogs only as being in group 1 or 2 (without breaking the code), after scrambling the order of patients within each group and removing identifying notations as to patient and clinic. For the final renal safety analysis, the code was broken 42 months after study initiation, when patient entry (n = 139) was complete. Before the code was broken, all identifying patient and clinic notations were again deleted, the order of patients within each group was scrambled, and statistical analyses were completed and conclusions drawn.

Age, sex distribution, and proportion of dogs that dropped out of the study were compared between groups (enalapril vs placebo) with t tests or $\chi^2$ tests. Serum creatinine and urea nitrogen concentrations at the time of enrollment (baseline) and at each recheck time (0.5 and approx 3, 6, 9, 12, 15, 18, 22, and 26 months) after initiation of treatment were compared between groups with t tests. In addition, repeated-measures ANOVA was performed to identify potential sources of variation within and between groups with respect to treatment, time, and the interaction of treatment and time. Serum creatinine and urea concentrations were plotted for each dog, and linear regression analysis was used to determine the rate of change in serum concentrations (ie, the slopes of the linear regression lines) from the time of enrollment to the final measurement. Slopes of the linear regression lines for dogs in each group were then compared with ANOVA. Proportions of dogs in each group in which serum creatinine or urea nitrogen concentration increased $\geq$ 35%, compared with concentration at the time of enrollment, and proportions of dogs in each group that developed azotemia (serum creatinine concentration $> 1.8$ mg/dl) were compared between groups with $\chi^2$ tests. For all analyses, values of $P \leq 0.05$ were considered significant.

Results

In total, 139 dogs were enrolled in the trial of enalapril efficacy (70 in the enalapril group and 69 in the placebo group). At the time of the present study, 55 of these dogs had completed the trial (ie, they had developed congestive heart failure), 36 had dropped out, and 48 were still enrolled in the trial. Reasons for dogs dropping out of the trial included death (2 in the enalapril group and 4 in the placebo group), death or euthanasia secondary to noncardiac disease (4 in the enalapril group and 7 in the placebo group), owner death or relocation (2 in the enalapril group), other disease (3 in the enalapril group and 3 in the placebo group), and owner noncompliance (5 in the enalapril group and 6 in the placebo group). In 1 dog, baseline serum creatinine and urea nitrogen concentrations were not available, because a blood sample was lost. In an additional 6 dogs, serum creatinine and urea nitrogen concentrations were not measured after initiation of enalapril treatment, because the dog completed or dropped out of the study before a second sample could be obtained. Therefore, 132 dogs were included in the present study (64 in the enalapril group and 68 in the placebo group).

For the present study, sex distribution of dogs in the enalapril group (50% males) was not significantly different from sex distribution of dogs in the placebo group (49% males); mean ± SD age of dogs in the enalapril group (10.0 ± 2.1 years) was not significantly different from mean age of dogs in the placebo group (10.5 ± 2.3 years); and mean body weight of dogs in the enalapril group (7.8 ± 3.5 kg [17.2 ± 7.7 lb]) was not significantly different from mean body weight of dogs in the placebo group (8.8 ± 4.4 kg [19.4 ± 9.7 lb]). In addition, proportion of dogs in the enalapril group that dropped out of the study (16/70) was not significantly different from the portion of dogs in the placebo group that dropped out of the study (20/69).

Serum samples were available from all 132 dogs at the time of enrollment in the study and 2 weeks after initiation of enalapril treatment. Because of dogs completing and dropping out of the study, serum samples were available from only 119 dogs (58 in the enalapril group and 61 in the placebo group) at 3 months, 102 dogs (50 in the enalapril group and 51 in the placebo group) at 6 months, 85 dogs (47 in the enalapril group and 38 in the placebo group) at 9 months, 69 dogs (36 in the enalapril group and 33 in the placebo group) at 12 months, 47 dogs (25 in the enalapril group and 22 in the placebo group) at 14 months, 35 dogs (20 in the enalapril group and 15 in the placebo group) at 18 months, 22 dogs (11 in the enalapril group and 11 in the placebo group) at 22 months, and 14 dogs (7 in the enalapril group and 7 in the placebo group) at 26 months. One dog in the enalapril group was azotemic.
(serum creatinine, 2.1 mg/dl) at the time of enrollment.

Mean serum creatinine concentrations were not significantly different between groups at any time during the study (Fig 1). Similarly, mean serum urea nitrogen concentrations were not significantly different between groups at any time (Fig 2). Neither group had a significant change in serum creatinine concentration, compared with baseline concentration, at any time during the study, and ANOVA did not reveal any change in serum creatinine concentration over time in either group. There was a statistically significant change in serum creatinine concentration over time in either group. The magnitude of this increase was small, equivalent between groups, and statistically unrelated to treatment.

Five dogs developed azotemia (serum creatinine concentration > 1.8 mg/dl) at 1 time point during the study. One dog in the enalapril group had a serum creatinine concentration of 2.6 mg/dl at 9 months, and 1 had a concentration of 2.1 mg/dl at 22 months. Two dogs in the placebo group had serum creatinine concentrations of 2.2 mg/dl at 3 and 15 months, and a third, with pyelonephritis, had a serum creatinine concentration of 4.9 mg/dl at 18 months.

There was no significant difference between groups in regard to proportion of dogs that had a ≥35% increase, compared with baseline concentration, in serum creatinine (12 dogs in the enalapril group and 17 in the placebo group) or serum urea nitrogen (40 dogs in the enalapril group and 37 in the placebo group).
function. Serum creatinine and urea nitrogen concentrations were used as indicators of renal function, as both can be easily measured in clinical practice and serum creatinine concentration has been shown to change from baseline concentration or the ratio of improved renal function and because a 30 to 40% decrease was considered to be indicative of a decrease in renal function in previous studies of human patients. Some evidence suggests that ACE inhibitor treatment may be of benefit in people at risk of heart failure. In addition, previous clinical trials9,10 of dogs with heart failure treated with benazepril or a placebo, the proportions of dogs that became azotemic or developed renal failure was not significantly different between groups. In fact, there are now data to suggest that renal function improves with ACE inhibitor treatment in humans, dogs, and cats with a variety of renal diseases, particularly those involving the glomerulus. Although the overall safety record of enalapril in veterinary medicine has been exemplary, studies in dogs have been relatively short-term (20 days to approx 4 months). In addition, the longest ACE inhibitor study9 (8 months) used a relatively low dosage of benazepril (starting dosage, 0.25 mg/kg, PO, q 24 h). The present study was designed to determine renal effects when enalapril was administered for a longer term at a clinically appropriate dosage to dogs with severe mitral regurgitation but without congestive heart failure (New York Heart Association class I or II). In 69 of the 132 dogs in this study, renal function was evaluated for at least 1 year after initiation of enalapril treatment, and in 14, renal function was evaluated for > 2 years.

The present study was part of an ongoing trial investigating whether enalapril could delay the onset of congestive heart failure in dogs with severe mitral regurgitation if treatment was instituted after evidence of left atrial enlargement was apparent but before pulmonary edema had developed. Previous studies2,3,21 have suggested that ACE inhibitor treatment may be of benefit in people at risk of heart failure. In addition, some evidence suggests that ACE inhibitors may help delay the onset of heart failure in dogs as well. Pederson et al22 demonstrated that the renin-angiotensin-aldosterone system was activated in Cavalier King Charles Spaniels with mitral regurgita-
tion but no or only mild clinical signs. O'Grady et al\(^4\) reported that Doberman Pinschers with subclinical dilated cardiomyopathy lived longer if they received an ACE inhibitor.

Although the present study was a part of a randomized controlled trial, there were, nevertheless, certain limitations. First, the number of patients was small, with < 70 dogs in each group. Second, although the duration of treatment was longer than in previous studies and germane to the life expectancy of aged dogs with heart disease, median follow-up time was only 12 months, and only 14 dogs were followed up for > 2 years. Third, these data apply to aged dogs with cardiomegaly secondary to mitral regurgitation and may not apply to dogs with other heart diseases or with certain pre-existing renal diseases. Fourth, the possibility that enalapril-induced improvements in hemodynamic status, with resultant increases in glomerular filtration rate, might have masked direct deleterious effects on renal function cannot be ruled out on the basis of results of the present study. Additionally, although there was no evidence of drug interactions in this study, concurrent drug treatments and their possible interactions with enalapril were not specifically monitored. Lastly, and most importantly, although serum creatinine concentration is the most specific of the common indicators of renal function, it and serum urea nitrogen concentration are relatively insensitive. Hence, mild alterations in renal function may not have been detected.


### References


