The Veterinary Journal 202 (2014) 573–577

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

The influence of enalapril and spironolactone on electrolyte concentrations in Doberman pinschers with dilated cardiomyopathy

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ARTICLE INFO

Article history:
Accepted 5 September 2014

Keywords:
Enalapril
Magnesium
Potassium
Cardiomyopathy
Spironolactone
Dog

ABSTRACT

The combination of an angiotensin-converting enzyme inhibitor (ACEI) with an aldosterone receptor antagonist can increase serum potassium and magnesium and lower serum sodium concentrations. The objective of this study was to retrospectively determine whether an ACEI and spironolactone can be co-administered to Doberman pinschers with occult dilated cardiomyopathy without serious adverse influences on serum electrolyte concentrations. Between 2001 and 2007, 26 client-owned Doberman pinschers were given enalapril, spironolactone, and carvedilol and followed for at least 6 months. Most dogs had been prescribed mexiletine for ventricular tachyarrhythmia suppression. Dogs were treated with pimobendan when congestive heart failure was imminent. Baseline and follow-up (3–10 visits) color-flow Doppler echocardiograms, serum urea nitrogen (SUN), creatinine, sodium, potassium, and magnesium concentration data were tabulated.

Compared to baseline data, there were no significant changes in serum sodium or serum creatinine concentrations. Serum magnesium ($P = 0.003$), serum potassium ($P = 0.0001$), and SUN ($P = 0.0001$) concentrations increased significantly with time. Although the combination of ACEI and spironolactone was associated with significant increases in magnesium, potassium, and SUN concentrations, these changes were of no apparent clinical relevance. At the dosages used in this study, this combination of drugs appears safe.

Introduction

Dilated cardiomyopathy is a common problem in Doberman pinschers (Calvert et al., 1982, 1997a, 1997b, 2000a, 2000b; Calvert and Brown, 1986; Smucker et al., 1990). In Doberman pinschers, there is a long subclinical or preclinical phase, the so-called occult phase, of disease progression which can be terminated by either sudden arrhythmic death (SAD) or congestive heart failure (CHF) (Calvert et al., 1982, 1997a, 1997b, 2000a, 2000b; Calvert and Brown, 1986; Smucker et al., 1990).

Drugs that have been demonstrated to exert a favorable influence on disease progression in humans with dilated cardiomyopathy include angiotensin converting enzyme inhibitors (ACEIs), spironolactone, and beta-adrenergic receptor blocking drugs (CONSENSUS Trial Study Group, 1987; SOLVD Investigators, 1992; Dahlström and Karlsson, 1993; RALES Investigators, 1996). In dogs, ACEIs have been shown to improve hemodynamic and quality of life indices (COVE Study Group, 1995; IMPROVE Study Group, 1995; Kitagawa et al., 1997; Ettinger et al., 1998). These studies mostly pertained to patients with CHF. The influence of beta-blockers or spironolactone on progression of CHF caused by dilated cardiomyopathy in dogs has not been reported. Recently, a retrospective study demonstrated that ACEIs may exert a positive influence on disease progression in Doberman pinschers with occult dilated cardiomyopathy (O'Grady et al., 2009).

There have been reports in humans of hyperkalemia, sometimes severe, associated with the co-administration of an ACEI and spironolactone (Barr et al., 1995; Berry and McMurray, 2001; Schepkens et al., 2001). For this reason, it has been recommended that these classes of drugs are not combined or only with caution and at low dosages (Greenblatt and Koch-Weser, 1973; Papich, 1995; Berry and McMurray, 2001; Schepkens et al., 2001). Although the safe administration of an ACEI and spironolactone has been reported in small dogs with myxomatous valvular disease without CHF, dogs with dilated cardiomyopathy are a unique cohort because of the greater potential of impaired kidney function through renal arterial underfilling and reduced renal blood flow secondary to low cardiac output via systolic dysfunction and/or arrhythmia (Desai et al., 2007; Thomason et al., 2007; Konstam et al., 2009). In humans, blockade of the renin–angiotensin–aldosterone system may induce worsening of renal function and more likely result in hyperkalemia in patients with reduced ejection fraction (Desai et al., 2007; Konstam et al., 2009).

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http://dx.doi.org/10.1016/j.tvjl.2014.09.004
1090-0233/

The purpose of this retrospective paper was to report the influence of the combination of enalapril and spironolactone on serum electrolyte concentrations administered to Doberman pinschers with occult dilated cardiomyopathy. Our hypothesis was that an ACEI and spironolactone can be co-administered to Doberman pinschers with occult dilated cardiomyopathy without serious adverse influences on serum electrolyte concentrations.

Materials and methods

Animals

The study population was comprised of 26 client-owned, previously untreated Doberman pinschers in which we diagnosed occult dilated cardiomyopathy by echocardiography and 24 h Holter recording between June of 2001 and December of 2007. The study dogs were presented for cardiomyopathy diagnostic screening tests. To that end, a color-flow Doppler echocardiogram and a 24 h Holter recording were performed on each dog at the first examination.

To be included in the study, each dog must have had an abnormal echocardiogram consistent with dilated cardiomyopathy (Calvert et al., 2000a, 2000b), >300 ventricular premature contractions (VPC) on 24 h Holter recording, and at least three follow-up examinations encompassing at least 6 months. Baseline and multiple follow-up samples were collected from each dog and tabulated. These samples included measurements of serum urea nitrogen (SUN), creatinine, potassium, magnesium, and sodium concentrations (Hitachi Serum Chemistry Analyzer; Roche Diagnostics). Follow-up visit samples were collected at approximately 1–5 month intervals.

Each dog was administered (1) spironolactone (Aldactone, GD Searle) at a dosage of 50 mg orally (PO) twice daily, (2) enalapril (Vasotec, Merck) at a dosage of 10 mg PO twice daily for 1 week and then a maintenance dosage of 20 mg PO twice daily, and (3) carvedilol (Coreg, SmithKline Beecham) at a dosage of 12.5 mg PO twice daily for 1 week and then increased to 25 mg PO twice daily. After 1 or 2 additional weeks, the dosage of carvedilol was increased to 37.5 mg PO twice daily for dogs weighing >35 kg. The dosages chosen were a product of dog and tablet sizes.

At the time of the study initiation, eight dogs were also administered mexiletine (Mexiletine, Boehringer Manheim Therapeutics) and mexiletine was later added to the treatment of 14 dogs. Mexiletine was administered when either rapid (>200 beats/min; bpm) ventricular tachycardia was detected or when >6000 ventricular premature complexes (VPC) per 24 h with couplets or triplets of VPC were detected by Holter recording. Mexiletine was given at either 150 mg ($n = 5$) or 200 mg ($n = 17$) PO three times daily.

At the time of initiation of the study, no dog was administered pimobendan (Vetmedin, Boehringer Manheim Therapeutics) but this was added later in some dogs where CHF was considered imminent i.e. when a gallop heart sound was auscultated, if nocturnal dyspnea was reported by the owner, and/or when echocardiographic data consistent with severe myocardial failure were present. Such echocardiographic data included left ventricular end-diastolic dimension >55 mm, fractional shortening <18% and E-point septal separation (EPSS) >15 mm. No further data were collected once furosemide was added to the treatment regimen.

Statistical methods

A repeated measures model that recognized multiple observations as belonging to the same dog was used to analyze SUN, serum creatinine, and serum electrolyte concentrations for changes over the follow-up period. Follow-up time (in weeks) and weight were included in the model as continuous variables. An unstructured covariance structure was used. All hypothesis tests were two-sided and the significance level was $P = 0.05$. The analysis was performed using PROC MIXED in SAS v.9.1.

Results

At the time of entry into the study, the mean (±SD, range) age of the dogs was 7.5 years (2.3, 5–12). There were 17 males and 9 females. The mean weight of the dogs was 36 kg (7.3, 28–45).

At the time of entry into the study, the mean (±SD, range) left ventricular end-diastolic dimension was 52 mm (2.8, 50–58), the mean left ventricular end-systolic dimension was 42 mm (2.5, 40–49), the mean left ventricular fractional shortening was 22% (2.2, 19–25), and the mean EPSS was 11.8 mm (1.7, 10–14).

The mean (±SD, range) dosages were for spironolactone 1.4 mg/kg twice daily (0.2, 1.1–1.6); for enalapril 0.56 mg/kg twice daily (0.1, 0.49–0.65); for carvedilol 0.89 mg/kg twice daily (0.1, 0.76–1.01); and for mexiletine 5.2 mg/kg three times daily (0.28, 4.3–6.1).

The normal reference ranges for renal values and electrolytes were SUN <31 mg/dL, creatinine <1.7 mg/dL, potassium 3.9–5.0 mmol/L, magnesium 1.6–2.4 mg/dL, and sodium 146–154 mmol/L. Baseline renal and electrolytes were as follows: (1) median (range) SUN 14 mg/dL (9–32); (2) mean serum creatinine 0.8 mg/dL (0.6–1.3); (3) median serum potassium concentration 5.1 mmol/L (4.4–6.2); (4) median serum magnesium concentration 2.1 mg/dL (1.9–2.6); and (5) median serum sodium concentration 148 mmol/L (138–152).

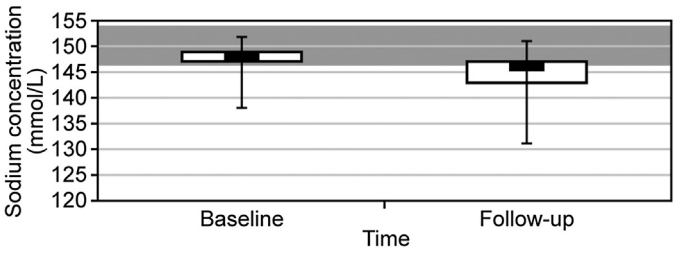

Fig. 1. Box and whiskers plot of the serum sodium concentrations in dogs at baseline (time 0 week; 26 dogs) and at follow-up (26 dogs) after the administration of an angiotensin-converting enzyme inhibitor (ACEI) and spironolactone. The bold line indicates the median. The boxes contain the 25–75th percentiles. The whiskers represent the 5th and 95th percentiles with lines below and above representing the 0–5th and 95–100th percentiles, respectively. There was no significant ($P < 0.05$) difference between baseline and follow-up serum sodium concentrations. Mean follow-up visit interval (±SD, range), 12 weeks (3.2, 8–20); mean follow-up visit number, 4.5 (1.8, 3–10).

Follow-up visit samples were obtained at a mean (±SD, range) of 12 week intervals (3.2, 8–20). The mean number of follow-up visits was 4.5 (1.8, 3–10).

There were no significant changes found in serum sodium ($P = 0.91$) or serum creatinine ($P = 0.68$) concentrations (Figs. 1 and 2). Serum magnesium ($P = 0.003$), serum potassium ($P = 0.0001$), and SUN ($P = 0.0001$) concentrations increased significantly with time (Figs. 3, 4, and 5). On at least one occasion, post-treatment SUN, potassium, and magnesium concentrations were above the reference ranges in 3 (12%), 13 (50%), and 4 (15%) dogs, respectively.

Discussion

The combination of enalapril and spironolactone at the dosages administered in Doberman pinschers with normal or nearly normal baseline serum creatinine and SUN was associated with significant increases in serum magnesium, serum potassium and SUN over time. This is not surprising considering that these drugs can individually alter serum electrolyte concentrations in this manner.

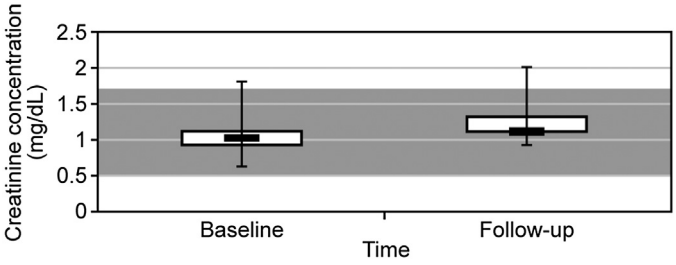

Fig. 2. Box and whiskers plot of the creatinine concentrations in dogs at baseline (time 0 week; 26 dogs) and at follow-up (26 dogs) after the administration of an angiotensin-converting enzyme inhibitor (ACEI) and spironolactone. The bold line indicates the median. The boxes contain the 25–75th percentiles. The whiskers represent the 5th and 95th percentiles with lines below and above representing the 0–5th and 95–100th percentiles, respectively. There was no significant ($P < 0.05$) difference between baseline and follow-up serum creatinine concentrations. Mean follow-up visit interval (±SD, range), 12 weeks (3.2, 8–20); mean follow-up visit number, 4.5 (1.8, 3–10).