Original Article

Evaluation of symptomatic improvements observed by switching to alacepril from other ACE-Inhibitors in dogs with mitral valve regurgitation

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Abstract

Alacepril is an ACE-inhibitor (ACE-I), which has unique properties including peripheral sympathoinhibitory effect and negative chronotropic effect, and it is suspected to have a superior cough suppressive effect in comparison to other ACE-Is. The purpose of the study was to evaluate whether switching to alacepril from other ACE-Is will alleviate the clinical symptoms of congestive heart failure (CHF) caused by mitral valve regurgitation (MR). The prospective clinical study included 73 client-owned dogs with MR that had been treated with ACE-Is other than alacepril for over a period of one month. The ACE-Is were replaced by alacepril and observed for four weeks. Parameters including heart rate (HR), body weight (BW), and general clinical conditions, such as activeness, appetite, responsiveness, and frequency of cough, were recorded before, and at two and four weeks after the switch. Each parameter was then statistically analyzed. Within four weeks of the switch, HR revealed a significant reduction, and clinical symptoms including activeness, appetite, responsiveness, and the frequency of cough showed significant improvements ($p<0.001$). Under this study condition, switching to alacepril from other ACE-Is has shown to reduce HR, and improve the clinical symptoms of CHF, in particular the frequency of cough.

Keywords: alacepril, cough, dogs, mitral valve regurgitation, prospective studies

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Introduction

Myxomatous mitral valve degeneration (MMVD) is the most common cardiovascular disease in dogs, and it is characterized by valvular degeneration of the mitral valve resulting in secondary MR (Atkins, et al., 2007; Borgarelli and Buchanan, 2012; Ishikawa, et al., 2010, Sisson, et al., 1999) . The prevalence of MMVD increases with age, and it shows breed predisposition in small breeds, such as Cavalier King Charles Spaniels, Chihuahuas, Cocker Spaniels, and Miniature Poodles (Borgarelli and Buchanan, 2012; Sisson, 1999). It is also more frequently observed in males (Borgarelli and Buchanan, 2012; Sisson, et al., 1999).

Angiotensin Converting Enzyme Inhibitors (ACE-Is) are potent vasodilators, which have been used for the treatment of CHF in s, and for hypertension and CHF in humans (Atkins, et al., 2007; BenchStudyGroup, 1999; Gordon and Kittleson, 2008; Ishikawa, et al., 2010; Kitagawa, et al., 1997; Kvart, et al., 2002; TheCOVEStudyGroup, 1995). The use of ACE-Is in dogs and humans with CHF has been associated with improvement of clinical symptoms and quality of life (Atkins, sco, et al., 2007; BenchStudyGroup, 1999; Ettinger, et al., 1998; Gordon and Kittleson, 2008; Kvart, 2002; TheCOVEStudyGroup, 1995). Numerous ACE-Is have been developed, with several of them available for the veterinary use. Most commonly used ACE-Is in dogs include benazepril, enalapril, and ramipril (Gordon and Kittleson, 2008). The primary difference between these drugs are the duration of effect and the potential side effects (Gordon and Kittleson, 2008). Several clinical trials have been conducted to evaluate the efficacy of some of these ACE-Is for the treatment of dogs with MMVD (Atkins, et al., 2007; BenchStudyGroup, 1999; Ettinger, et al., 1998; Kitagawa, et al., 1997; Kvart, et al., 2002; TheCOVEStudyGroup, 1995).

Alacepril is a mild, long-acting, sulphydryl-containing ACE-Is, with unique properties including peripheral sympathoinhibitory effect and negative chronotropic effect (Kinugawa, et al., 2002; Matsuno, et al., 1986; Ogihara, et al., 1992; Takeyama, et al., 1986). Alacepril is desacetylated to form desacetylalacepril (DU-1227), which is then converted to captopril (Kinugawa, et al., 2002; Matsuno, et al., 1986; Ogihara, et al., 1992). In addition, alacepril is superior in left atrial pressure-reducing effects (Ishikawa, et al., 2010). Even though alacepril has been widely used in dogs for the treatment of MMVD in Japan, limited information is available on the clinical efficacy of alacepril. Additionally, the superior cough suppressive effect of alacepril had been suggested, however, it remains anecdotal. Therefore, the purpose of the study was to evaluate whether switching to alacepril from other ACE-Is would alleviate the clinical symptoms of CHF, including the frequency of cough, in dogs with MR secondary to MMVD.

Materials and Methods

Selection of dogs: The prospective clinical study was carried out in collaboration with over 45 first opinion veterinary practices throughout Japan. The dogs were client-owned, and had been receiving treatments for the MR secondary to MMVD. Dogs were eligible for inclusion if they had been treated with ACE-Is other than alacepril for over a period of one month. Since most of the dogs receiving treatment for MR had been medicated with a combination of drugs, concomitant use of other drugs including diuretics was allowed under the condition that the combination of drugs and the dosages would not be changed during the period of the study.

Study design: The ACE-Is were replaced by alacepril (DS Pharma Animal Health Co., Ltd. Japan), with the dosage of alacepril adjusted based on the dosage of the previously used ACE-Is (Table 1). The dosage of alacepril was set based on the dosage of the other ACE-Is stated on the respective drug leaflets. The clinical study was conducted for four weeks, with veterinary visits at the beginning of the study (baseline), and at the end of week 2 and week 4. Clinical parameters including HR and BW were measured at the baseline, and at weeks 2 and 4 of the study. HR was measured by use of auscultation with a single count strategy of 30 seconds. General clinical conditions including activeness, appetite, responsiveness, and the frequency of cough were scored from 0 to 3, with the assessment criteria for each parameters listed in table 2. These parameters were also recorded at the baseline, and at week 2 and 4. For the assessment of disease condition, ISACHC classification was used to determine the severity of the CHF (International Small Animal Cardiac Health Council, 1994). The Levine scale (Silverman and Wooley, 2008) was used to classify the degree of cardiac murmur, and thoracic radiography or echocardiography was used to classify ISACHC. These assessments were performed at baseline and at week 4.

Table 1 ACE-Is dose conversion table.

Previously used ACE-Is			Converting dose of Alacepril
Benazepril	0.2mg	→	1mg
Enalapril	0.2mg	→	1mg
Ramipril	0.1mg	→	1mg
Temocapril	0.04mg	→	1mg

List of adjusted dosage of alacepril for each of the previously used ACEI including benazepril, enalapril, and temocapril.

Statistical analysis: Data are expressed as mean ± SD for the continuous variables, and as mean for the ordinal variables. Statistical analyses were performed using statistical software (Prism 5.0v, GraphPad Software Inc., USA). To evaluate the changes in parameters between the weeks, paired student's t test was used for the parametric variables and Wilcoxon

signed rank test was used for the non-parametric variables.

The study group was further subdivided into three groups based on the previously used ACE-Is into benazepril, enalapril, and temocapril. To evaluate the changes in parameters between the weeks for each treatment groups, paired student's t test was used for the parametric variables, and Wilcoxon signed rank test was used for the non-parametric variables. Unpaired student's t test was used for the parametric variables and Mann-Whitney U test was used to ensure that there are no significant differences amongst the treatment groups at the baseline. Significant difference was defined as $P < 0.05$.

Table 2 Assessment criteria for general clinical conditions.
Clinical symptoms including activeness, appetite, responsiveness, and the frequency of cough were scored from 0 to 3 accordingly to the assessment criteria.

General Clinical Condition		
Parameters	**Scores**	**Assessment criteria**
Activeness	0	Normal
	1	Loss of activeness during or after a strenuous exercise
	2	Loss of activeness during or after a light exercise
	3	Loss of activeness even at rest
Appetite	0	Normal
	1	Reduction of daily food intake by about 1/4
	2	Reduction of daily food intake by more than 1/2, with one day a week without food
	3	2 to 3 days a week without food
Responsiveness	0	Normal, respond to stimuli
	1	Slightly depressed, relatively limited movement but respond to stimuli
	2	Depressed, notice stimuli but lacks in response
	3	Does not respond to stimuli, exhausted and recumbent
Frequency of cough	0	No cough (Normal)
	1	Cough during exercise, or cough rarely at rest
	2	Frequently cough at rest
	3	In addition to above, paroxysmal cough is observed

Results

Seventy-three client-owned dogs with MR secondary to MMVD that had been treated with ACE-Is other than alacepril for over a period of one month had been enrolled in the study. The study group consisted of 48 males and 25 females, with the mean age of 11.86 ± 2.48 years. The average body weight was 5.59 ± 2.91 kg, and the dog breeds consisted of the following; 15 were of Shih Tzu; 10 were Chihuahuas; 9 each were Maltese and Pomeranians; 6 were Cavalier King Charles Spaniels; 5 were mixed breeding; 4 each were miniature dachshund, Papillion, and Toy poodles; 2 were Yorkshire Terriers; and 1 each were Beagle, Miniature Schnauzer, Pekingese, Shetland Sheepdog, and Shiba. Of these 73 dogs, only 34 dogs were on ACE-Is only treatments, and the remaining 39 dogs were on combination of drugs including diuretics (furosemide, spironolactone, and azosemide), aminophylline, digoxin, isosorbide mononitrate, pimobendan, and theophylline. As for the ACE-Is, 26 dogs were taking enalapril, 23 dogs were taking benazepril, another 23 dogs were taking temocapril, and only one dog was taking ramipril (Table 3).

The HR revealed significant reduction within the 4 weeks of treatment ($p<0.0001$), were most significant reduction was observed between week 2 to 4 ($p=0.0021$) (Figure 1). The BW showed significant gain by week 2 ($p=0.0088$), which then showed significant reduction at week 4 in comparison to baseline ($p=0.0073$). Clinical symptoms including activeness, appetite, and responsiveness showed significant improvement by week 2 ($p=0.0029$, 0.0012, and 0.0004, respectively). The frequency of cough had also shown significant reduction from week 2 ($p<0.0001$) (Figure 2).

No significant differences were observed when the baseline values of each parameter were compared between the three treatment groups. Reduction of HR was observed in both enalapril and temocapril ($p=0.0025$), however, only enalapril showed significant changes from week 2 ($p=0.0435$) (Figure 3). Temocapril was the only treatment group that showed significant changes in BW, which the reduction of BW was observed from week 2 ($p=0.0016$). Improvement in activeness was observed in both enalapril and temocapril from week 2 ($p=0.3269$, 0.0369, respectively). Improvement in appetite was only observed in enalapril, which was only within the first 2 weeks of treatment ($p=0.0477$). Improvement in responsiveness was observed in both enalapril and temocapril, which only temocapril showed improvement from week 2 ($p=0.0197$). All three-treatment groups showed significant reduction in the frequency of cough from week 2 (Figure 4).

At the baseline examination, 1 dog was classified as Ia, 6 dogs as Ib, 39 dogs as II, 25 dogs as IIIa, and 2 dogs as IIIb of the ISACHC classification. After receiving 4 weeks of alacepril, the dogs classified as Ib had increased to 19 dogs, II to 40 dogs, IIIa had declined to 10 dogs, and none of the dogs were classified as IIIb. As for the Levine scale, at the baseline, 2 dogs were classified as scale of I/VI, 4 dogs as II/VI, 21 dogs as III/VI, 23 dogs as IV/VI, 18 dogs as V/VI, and 5 dogs as VI/VI. A the end of the study, the number of dogs classified as scale II/VI had increased to 6, III/VI to 22, and V/VI had decreased to 12.

Table 3 Clinical parameters and general clinical conditions.

Groups	n	Parameters	Baseline	Week 2	Week 4
	73	**BW (kg)**	5.59 ± 2.91	5.67 ± 2.97†	5.50 ± 3.00†
		HR (bpm)	129.63 ± 27.80	127.37 ± 28.68	122.04 ± 27.41‡||
		Activeness	1.19	0.99†	0.76‡¶
		Appetite	0.48	0.29†	0.22†
		Responsiveness	0.77	0.54‡	0.47‡
		Cough	1.86	1.13‡	0.93‡||
Benazepril	26	**BW (kg)**	5.06 ± 1.85	5.39 ± 1.78	5.00 ± 4.11
		HR (bpm)	128.48 ± 29.31	127.17 ± 29.75	122.52 ± 29.02
		Activeness	1.22	0.90	0.83
		Appetite	0.48	0.35	0.22
		Responsiveness	0.70	0.50	0.52
		Cough	1.78	0.95†	0.74‡
Enalapril	23	**BW (kg)**	5.47 ± 3.88	5.51 ± 4.11	5.46 ± 4.11
		HR (bpm)	127.04 ± 26.51	122.61 ± 29.54*	119.19 ± 25.88†
		Activeness	1.04	0.92*	0.6†§
		Appetite	0.54	0.33*	0.24
		Responsiveness	0.69	0.46	0.44*
		Cough	1.81	1.04‡	0.92‡
Temocapril	23	**BW (kg)**	6.20 ± 2.53	6.04 ± 2.50†	5.99 ± 2.53†
		HR (bpm)	133.39 ± 29.19	132.35 ± 28.06	124.70 ± 28.98†§
		Activeness	1.30	1.09*	0.87†§
		Appetite	0.39	0.17	0.22
		Responsiveness	0.91	0.65*	0.48†
		Cough	2.00	1.39†	1.13‡§

Clinical parameters including BW and HR, and general clinical conditions including activeness, appetite, responsiveness, and the frequency of cough, are expressed as mean ± SD for the continuous variables, and as mean for the ordinal variables. * p<0.05; † p<0.01; ‡ p<0.001 compared to the corresponding baseline values. § p<0.05; || p<0.01; ¶ p<0.001 compared between week 2 and 4.

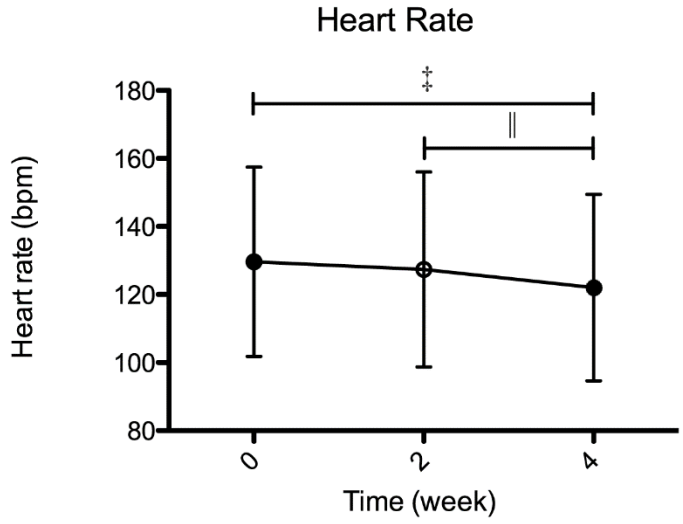

Figure 1 Changes in HR (mean ± SD) observed with the switch to alacepril. Significant reduction was seen within 4 weeks of treatment, and most significant reduction was observed between week 2 to 4. ‡ p<0.0001 compared to the baseline. || p<0.01 compared between week 2 and 4.

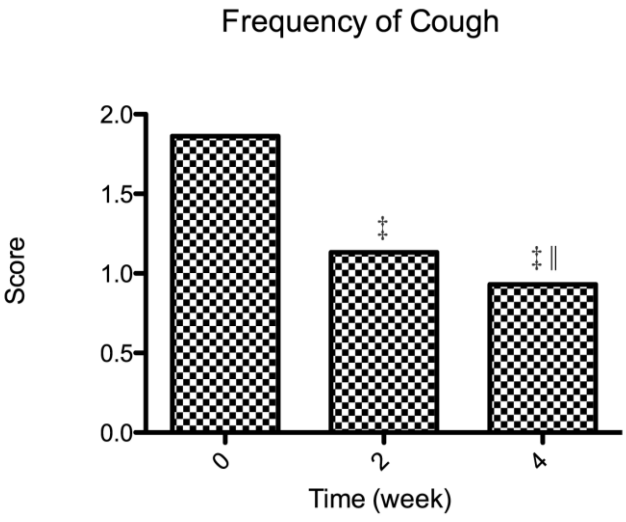

Figure 2 Changes in the frequency of cough (mean) observed with the switch to alacepril. Significant reduction was observed from week 2. ‡ p<0.0001 compared to the baseline. || p<0.01 compared between week 2 and 4.

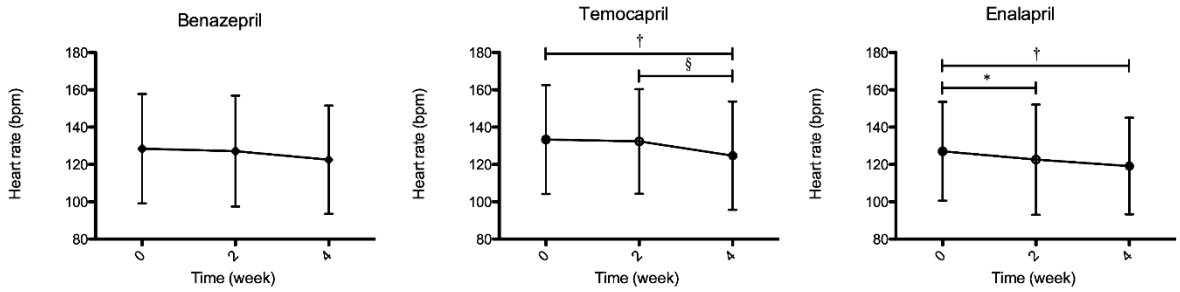

Figure 3 Changes in HR (mean ± SD) observed with the switch to alacepril evaluated based on previously used ACEIs; benazepril, enalapril, and temocapril. Significant reduction of HR was observed in both enalapril and temocapril. * $p<0.05$; † $p<0.01$ compared to the corresponding baseline values. § $p<0.05$ compared between week 2 and 4.

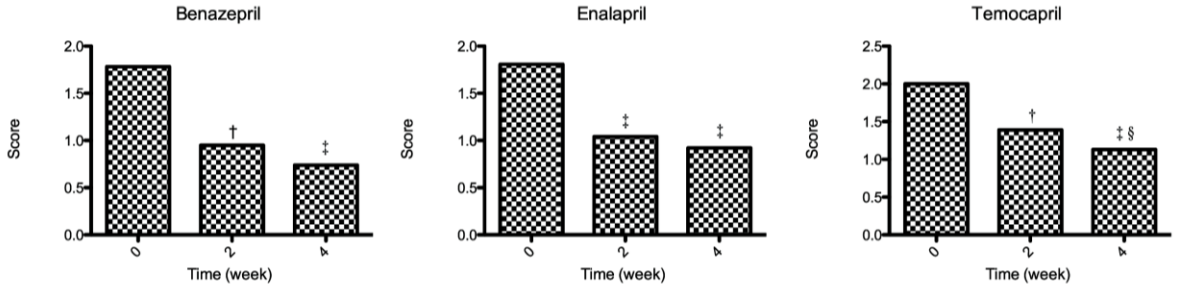

Figure 4 Changes in the frequency of cough (mean) observed with the switch to alacepril evaluated based on previously used ACEIs; benazepril, enalapril, and temocapril. All three-treatment groups showed significant reduction in the frequency of cough from week 2. † $p<0.01$; ‡ $p<0.001$ compared to the corresponding baseline values. § $p<0.05$ compared between week 2 and 4.

Discussion

This study was a large-scale prospective clinical trial involving over 45 first opinion veterinary practices throughout Japan. The study group consisted mainly of elderly, small breed dogs, with over two thirds of the dogs were male, and it was consistent with the typical demographic of the canine MVDD. More than half of the dogs in the study were taking combination of drugs for the treatment of CHF. There have been several studies in the past, which have shown positive effect of treatment with ACE-Is in combination with standard therapy of CHF on the clinical symptoms and duration of clinical stability in dogs with symptomatic MMVD (BenchStudyGroup, 1999, Ettinger, Benitz, Ericsson, Cifelli, Jernigan, Longhofer, Trimboli and Hanson, 1998, TheCOVEStudyGroup, 1995). This study is unique that the dogs had already been treated with ACE-Is prior to the study. It was designed to observe the effect of switching from one ACE-Is to another, which has never been tested before.

Significant reduction of HR was observed by switching to alacepril from other ACE-Is in dogs with MR. This result was consistent to that of Ishikawa et al., who reported that significant HR reduction with alacepril was observed in dogs with experimentally induced MR when compared with enalapril (Ishikawa, Tanaka, Suzuki, Miyaishi, Akagi, Iino, Fukushima and Yamane, 2010). Since captopril, the precursor of alacepril, has been shown to improve the vagal activity in dogs with CHF and enhance vagally mediated bradycardia in rats, Ishikawa et al. suggests the negative chronotropic effect of alacepril to be of vagal influence (Ishikawa, Tanaka, Suzuki, Miyaishi, Akagi, Iino, Fukushima and Yamane, 2010, Osterziel, Dietz, et al., 1990, Takata, Arai, et al., 2004). Additionally, several preclinical studies have shown sympathoinhibitory effect of alacepril caused by its metabolite, DU1227, which could be responsible for the HR reduction observed in this study (Matsuno, Taira, Fujitani, Ito and Kadokawa, 1986, Ogihara, Tachi and Uno, 1992). This study revealed alacepril to have a significant negative chronotropic effect, and although it is only a speculation, this negative chronotropic effect of alacepril is most likely to be multifactorial.

Switching to alacepril from other ACE-I has resulted in significant improvement of the clinical symptoms in dogs with MR. Improved clinical symptoms included activeness, appetite, responsiveness, and the frequency of cough, which were all observed from week 2. The BENCH study and the COVE study demonstrated similar results, which treatments with benazepril and enalapril respectively, resulted in significant clinical improvement (BenchStudyGroup, 1999, TheCOVEStudyGroup, 1995). The BENCH study revealed a 72.3% global clinical improvement at as early as day 7 of the study. However, it included the results of both dogs with MMVD and dilated cardiomyopathy (DCM), which could have influenced the result (BenchStudyGroup, 1999). On the other hand, in the COVE study, significant clinical improvement was only detected at day 28 of the study with enalapril (TheCOVEStudyGroup, 1995). Based on these results, the timing of the clinical improvement may differ depending on the ACE-Is used, and alacepril appears to have a relatively fast effect on the clinical symptoms.

The degree of effect of alacepril on the dogs with MR differed depending on the ACE-Is used before the switch. The most significant changes were observed with enalapril and temocapril groups, where

significant changes were observed in all parameters, except for the BW in enalapril group and appetite in temocapril group. On the other hand, the frequency of cough was the only parameter that showed significant change in benazepril group. It is also important to note that the frequency of cough was the only parameter that resulted in significant improvement in all three-treatment groups. Although cough suppressive effect of alacepril has never been documented before, several possibilities can be considered from previous studies. Alacepril is known to have a sympathoinhibitory effect, which may have resulted in relaxation of the bronchial smooth muscle (Matsuno, Taira, Fujitani, Ito and Kadokawa, 1986, Ogihara, Tachi and Uno, 1992). Also, Ishikawa et al. have demonstrated alacepril to reduce left atrial pressure (LAP) in dogs with experimentally induced MR. Similar reduction in LAP may have relieved the bronchial compression caused by the enlarged left atrium in this study, resulting in reduced frequency of cough. These results provide objective evidence that alacepril has a potent cough suppressive effect, and with the results of this study, one can only speculate that the cough suppressive effect of alacepril is most likely to be multifactorial.

4 weeks of treatment with alacepril had shifted the number of dogs classified from higher classes to lower classes of ISACHC classification, and overall reduction of murmur intensity was observed. Similarly, Kinugawa et al. demonstrated improvement of disease severity assessed by NYHA classification after treatment with alacepril in humans. This improvement of disease severity was accompanied by improvement of the radiographic and echocardiographic evaluations. Although an objective evaluation of the disease condition was not performed in this study, these results suggest switching to alacepril resulted in improvement of disease severity as observed with the ISACHC classification, and improvement of the clinical symptoms are relates to the improved disease condition.

Limitation of this study includes lack of objective evaluation of MR. In the study, ISACHC classification was used for the evaluation of the disease severity. However, ISACHC classification is a subjective method, and it cannot be used as a substitute for an objective assessment. Radiographic and echocardiographic evaluations were included in the parameters to be examined, however, they were not mandatory. Therefore, radiographic and echocardiographic evaluations were only completed in 25 dogs and 2 dogs respectively. However, as suggested above, there seems to be a strong correlation between the improvement of the clinical symptoms and the disease severity. Therefore, although additional objective evaluation using radiographic and echocardiographic tests would have been desirable, lack of them did not adversely affect the results.

In this study, witching to alacepril from other ACE-Is has shown to reduce HR, and improve the clinical symptoms of CHF, in particular the frequency of cough. The improvement of the clinical symptoms was related to the improvement in the class of heart failure. In addition to the influence on the renin-angiotensin-aldosterone system (RAAS), alacepril is known to have a wide range of actions, including inhibitory effects on the sympathetic nervous system and negative chronotropic effects. Although with the results of this study one cannot be certain, however, it is most likely that multiple factors are involved in the chough suppressive effect of alacepril.

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บทคัดย่อ

การประเมินอาการ จากการใช้ alacepril แทน ACE-Inhibitors ชนิดอื่น ๆ ในสุนัขที่มีภาวะหัวใจล้มเหลวที่เกิดจากลิ้นหัวใจชนิด mitral

*อากิโก๊ะ อูมูระ ลินา ฮามาเบ้ คาซูมิ ชิมาดะ มิกิ ชิมิซู ไรยู ทานากะ**

Alacepril มีคุณสมบัติยับยั้ง ACE (ACE-I) โดยมีผลต่อ peripheral sympathoinhibitory และผล chronotropic ในทางลบ รวมทั้งมีผลในการยับยั้งการไอได้ดีกว่ายา ACE-Is ชนิดอื่น ๆ วัตถุประสงค์ของการศึกษาคือ การประเมินว่าการเปลี่ยนไปใช้ยา alacepril จาก ACE-Is ชนิดอื่น ๆ จะช่วยบรรเทาอาการทางคลินิกของภาวะหัวใจล้มเหลว (CHF) ที่เกิดจากลิ้นหัวใจชนิด mitral (MR) หรือไม่ การศึกษาทางคลินิกในสุนัขจำนวน 73 ตัว ที่เคยได้รับการรักษาด้วยยา ACE-Is ที่ไม่ใช่ยา alacepril นานหนึ่งเดือน และเปลี่ยนมาใช้ยา alacepril แทนที่ ACE-Is เป็นเวลาสี่สัปดาห์ และสังเกตอาการทางคลินิก อัตราการเต้นของหัวใจ (HR) น้ำหนักตัว (BW) และสภาวะทางคลินิกทั่วไป เช่นความกระตือรือร้น ความกระปรี้กระเปร่า การตอบสนอง และความถี่ของอาการไอ โดยจดบันทึก ณ ก่อนเปลี่ยนยา สองสัปดาห์ และสี่สัปดาห์หลังการเปลี่ยนยา ผลการวิเคราะห์ทางสถิติพบว่า อัตราการเต้นของหัวใจลดลงอย่างมีนัยสำคัญ และอาการทางคลินิกรวมทั้งความกระตือรือร้น การตอบสนอง และความถี่ของอาการไอ ดีขึ้นอย่างมีนัยสำคัญ ($p < 0.001$) จากการศึกษานี้แสดงให้เห็นว่า การใช้ alacepril แทน ACE-Is ชนิดอื่น ๆ มีผลต่อการลดอัตราการเต้นของหัวใจ และอาการทางคลินิกของภาวะหัวใจ ล้มเหลวดีขึ้น โดยเฉพาะความถี่ของไอ

คำสำคัญ: ไอ สุนัข ลิ้นหัวใจชนิด mitral การศึกษาไปข้างหน้า

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