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Effects of ivabradine on left ventricular function in dogs with congestive heart failure

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Original Article

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Abstract

Ivabradine is an essential drug administered in current standard therapy for human heart failure and is expected to be beneficial to congestive heart failure dog. Ivabradine is a selective I_f Channel inhibitor. It reduces cardiac pacemaker activity and slows heart rate. There are a few reports of ivabradine in veterinary applications. The aim of this study was to investigate the effects of ivabradine on left ventricular function in dogs with congestive heart failure. Thirteen client-owned dogs with systolic and/or diastolic heart failure were included in this study. The dogs were assigned to two groups: (i) the active control group, given propranolol at 0.5 mg/kg, and (ii) the group treated with ivabradine at an initial dose of 0.5 mg/kg twice a day for 7 days, followed by a maintenance dose of 0.3 mg/kg twice a day. Types of arrhythmias were confirmed by lead II ECG, blood pressure, and echocardiography were measured before and 15 and 30 days after treatment of ivabradine. Results showed decrease in heart rate and improvement in score of quality of life. Ejection fraction and left ventricular size remained normal. These results indicate that the treatment with ivabradine can decrease heart rate and improve quality of life in dogs with congestive heart failure with no adverse effects on cardiac contractility.

Keywords: ivabradine, antiarrhythmic drug, congestive heart failure, cardiac function, dog

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Introduction

Heart failure is a symptom consisting of abnormalities of either the structure or the function of the heart. The heart is unable to pump a sufficient amount of blood to meet a metabolic need. A number of compensatory responses are stimulated to preserve cardiac output, including excessive tachycardia, sodium and water retention, vasoconstriction and cardiac remodeling. The goal of heart failure treatment is to reduce the symptoms and improve quality of life. Medications along with diet management are used to control fluid balance and to limit cardiac remodeling. Heart failure should be treated routinely with four medications such as angiotensin converting enzyme (ACE) inhibitor, diuretic, inotrope agent and beta blocker. Beta blocker is a medicine that can be used to treat many conditions including reduced heart rate. However, non-selective beta blockers such as propranolol may have undesirable side effects such as decreased arterial blood pressure and contractility (Gorre & Vandekerckhove, 2010).

Ivabradine is a new heart rate reducing agent that seems to beat the previous drug limitations. Ivabradine is a selective sinus node I_f Channel inhibitor which is known as a pacemaker current (Na^+ -K^+ inward current). Previous studies reported that ivabradine could reduce heart rate and rhythm without interfering other aspects of the cardiac function (Bois P, 1996; Di Francesco D, 2003; Gardiner SM, 1995; Thollon C, 1994). Moreover, a recent study showed that ivabradine could reduce heart rate without altering other systems especially contractility of the heart, which is a key in the treatment of heart failure (Franke et al., 2011). Many studies demonstrated that ivabradine could be used in combination with a beta blocker in patients with respiratory problems (Chaitman, 2004; Stieber, 2008; Riesen, Schober, Cervenec, & Bonagura, 2012; Sabbah et al., 2011). However, the precise mechanism and effect of ivabradine to treat dogs with congestive heart failure remain unclear. The purpose of this study was to determine the efficacy of ivabradine in dogs with congestive heart failure by means of a clinical trial. It was hypothesized that the use of ivabradine to modulate heart rate would be useful in dogs with congestive heart failure.

Materials and Methods

Animals: This study was performed in clinical cases at Kasetsart Veterinary Teaching Hospital, Kamphaeng Saen. All procedures used in this study were approved by Animal Care and Use Committee of Kasetsart University. Thirteen dogs demonstrating pretreatment clinical signs of congestive heart failure of stage C according to ACVIM classification system (Atkins et al., 2009) were recruited into the study. The breeds included Poodle, Shih Tzu, and cross-bred. Body weight ranged from 3 to 16 kg. All dogs were required to have normal or unremarkable hematology and chemistries prior to enrollment. Each dog demonstrated cardiac murmur, abnormal cardiac structure from chest radiography, and cardiac arrhythmias. Owners provided their consent prior to enrollment and completed take-home questionnaires on their dogs' quality of life during the study period.

Treatments: Each dog received standard cardiac medications for heart failure, including diuretics and ACE inhibitors. The owners were asked to schedule clinical evaluation. The dogs were randomly divided into two groups, consisting of control group and ivabradine group. The control dogs (Control, n=7) were given standard treatment for heart failure and beta adrenergic blocker for antiarrhythmic agents. The dogs in ivabradine group (Iva, n=6) were given standard treatment for heart failure and ivabradine for antiarrhythmic agents. The initial dose of ivabradine was 0.5 mg/kg twice a day for 1 week, then the dose was reduced to 0.3 mg/kg twice a day. The end points in this study involved quality of life and echocardiographic parameters.

Electrocardiography examination: Electrocardiogram was recorded from the lead II to evaluate heart rate and heart rhythm. Dogs with specific types of arrhythmias such as sinus tachycardia with a resting heart rate of more than 120 beats per minute (bpm) were included in the study.

Echocardiography examination: Each dog underwent a transthoracic echocardiography with continuous electrocardiogram monitoring (General Electric (GE) Medical System, vivid5s, Germany) to confirm the diagnosis and to monitor the disease progression. The measurement was performed in parasternal long, short axis views and apical four-chamber view when the dog was on right and left lateral recumbency with no sedation. Echocardiography was evaluated before and after medications by one skillful sonographer. Echocardiographic images were captured and stored for offline analysis. Left ventricular wall structure and function were calculated by measuring the images from two-dimensional and M-mode planes. Cardiac dimensions were measured during diastole and systole to obtain parameters such as IVSd, diastolic interventricular septum thickness; IVSs, systolic interventricular septum thickness; LVIDd, left ventricular end diastolic diameter; LVIDs, left ventricular end systolic diameter; LVPWd, left ventricular wall diastolic thickness; and LVPWs, left ventricular wall systolic thickness. The following calculation was performed to index the left ventricular ejection fraction (EF) as:

$$EF = [(EDV - ESV) / EDV] \times 100$$

Diameter of left atrium (LA) and aortic root (AO) and the ratio (LA/AO) were assessed from M-mode view at the level of the aorta when the aortic and pulmonic valves were closed during diastole. Mitral regurgitation jet area was determined by continuous-wave color flow Doppler echocardiography using the left apical 4-chamber view.

Thoracic radiography: Two orthogonal views were performed and evaluated on all dogs. Vertebral heart score (VHS) was measured in the left lateral view as shown in Figure 2. Lung pattern was recorded and evaluated on all dogs at day 0 and day 30 after the initiation of treatment.

Blood pressure measurement: Blood pressure measurement using Doppler transducer was performed in triplicate in all dogs.

Evaluation: All dogs were subjected to clinical evaluation including physical examination, routine hematology and blood chemistry, blood pressure measurement, thoracic radiography, electrocardiography and echocardiography. Exclusion criteria included systolic blood pressure < 90 mmHg. The owners were also asked to assess their animals' activity and complete questionnaires adapted from Minnesota living with heart failure and validation of a survey for quality of life assessment. They were asked to score the dogs' physical function, happiness, mental status and hygiene by means of ordinal numbers in which high scores indicated the worst quality of life as shown in Table 1. Follow-ups were 15 and 30 days after the the first visit. The sequence of the study appears in Figure 1. All dogs were evaluated by one veterinarian throughout the study.

Table 1 Domains and assessment items in questionnaire. Each domain contains related items that were scored on a scale of 0 to 5, where 0 is minimum level and 5 is maximum level.

General health assessment	Description
Physical function	(1) My dog rests and sleeps all day long.
	(2) My dog lays in one place all day long.
	(3) My dog moves normally.
	(4) My dog is in pain.
	(5) My dog coughs and pants frequently even at rest.
	(6) My dog has swelling on legs and ascites.
	(7) My dog shows side effect from medications.
Happiness	(1) My dog wants to play.
	(2) My dog reacts to my presence.
	(3) My dog enjoys life.
Mental status	(1) My dog shakes or trembles.
	(2) My dog seems depressed and not alert.
Hygiene	(1) My dog keeps him/herself clean.
	(2) My dog smells like urine or has skin irritation.
	(3) My dog's hair is greasy and rough.

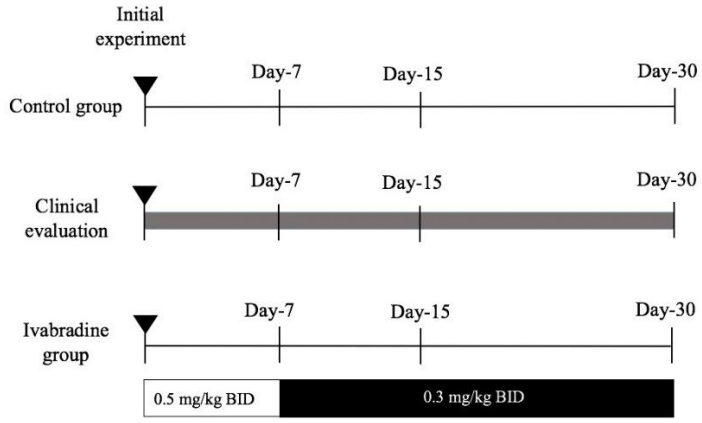
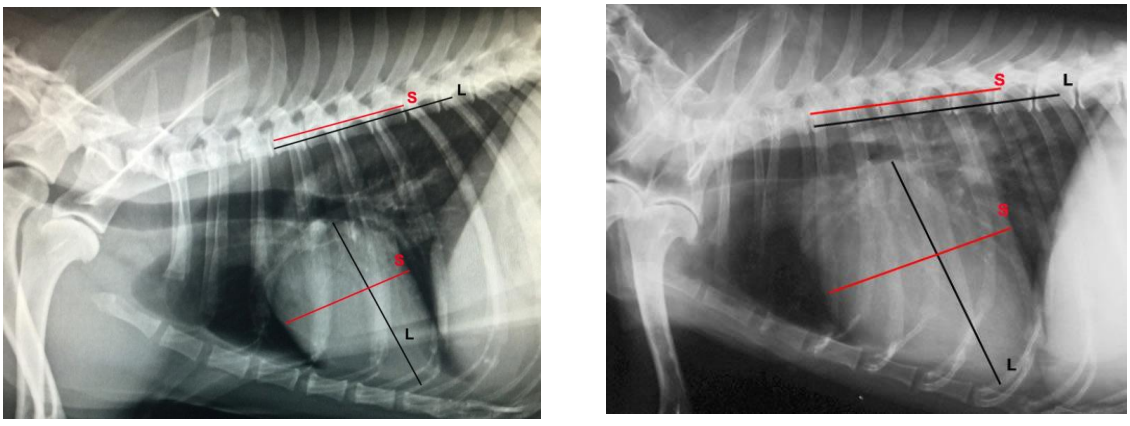


Figure 1 Clinical trial sequence



Normal (range 9.7±0.5)
VHS = L + S = 5.5 + 4 = 9.5

Cardiomegaly
VHS = L + S = 6.75 + 5.25 = 12

Figure 2 Radiographic findings present heart remodeling. VHS was calculated as the sum of 2 measurements from long axis line (L) and short axis line (S).

Statistical analysis: Continuous variable showed as mean ± standard error (SE). Statistical analysis was performed using commercially available software (GraphPad Software Inc., USA). Comparison was performed using 2-way ANOVA for repeated measures. A value of $p<0.05$ was considered statistically significant.

Results

General characteristics: Clinical characteristic is shown in Table 2. The dogs in the control (n=7) and ivabradine-treated groups (n= 6) had average ages of 11.43±0.7 and 13.8±0.9 and average weights of 6.4±1.1 and 9.1±2.2, respectively. The dogs were 5 Poodles, 2 mixed breeds, 3 Shih Tzus, 2 Miniatures, and 1 Pomeranian. All dogs were in heart failure stage C. The dogs in both groups were well matched with respect to general characteristics such as radiographic and echocardiographic as shown in Table 2.

Thoracic radiographic findings: The average vertebral heart score (VHS) from the radiograph of dogs was statistically non-significant after treatment. VHSs in the control and ivabradine-treated groups were 12.09±1.72 and 13.2±1.93, respectively. Four dogs had pulmonary edema, 4 dogs had interstitial lung pattern, 1 dog had bronchial lung pattern and 4 dogs had mixed lung pattern. The vertebral heart score did not significantly change after treatment.

Effects on blood pressure: The percentage changes of blood pressure are summarized in Table 3. The pre-treatment valves were 151.75±8.6 mmHg for the control group and 133.5±5.1 for the ivabradine group. After 15 days of treatment, in the control group, the dose of 5 mg/kg daily decreased the systolic blood pressure by 9.39%, whereas no significant change was detected in the ivabradine group.

Table 2 Database of echocardiographic, hemodynamic, radiographic, and biochemical characteristics of dogs treated with ivabradine (IVA) and propranolol (Control). Values reported as mean±SEM.

	Baseline		
	Control (n=7)	**IVA (n=6)**	***P***
Echocardiography			
LVIDs (cm)	2.29±0.27	2.20±0.24	0.25
LVIDd (cm)	3.31±0.33	3.50±0.32	0.22
LA:Ao	1.76±1.22	2.00±0.42	0.30
FS (%)	31.0±3.63	32.14±2.80	0.48
EF (%)	58.86±5.54	61.0±4.23	0.39
Blood pressure (mmHg)			
Systolic	151.75±8.64	133.5±5.07	0.08
Heart rate (bpm)	150±8.16	169.43±10.12	0.13
Radiographic			
VHS	12.19±0.70	13.2±1.1	0.23
Blood work			
BUN	33.09±12.34	23.9±4.5	0.20
Creatinine	1.05±0.22	0.9±0.06	0.19
Quality of life			
Physical functioning	8.25±0.63	7.5±0.65	0.22
Happiness	4.0±1.08	4.0±1.04	0.18
Mental status	2.0±0.70	1.25±0.48	0.21
Hygiene	0.6±0.27	1.5±0.29	0.03

LVIDd, left ventricular end diastolic diameter; LVIDs, left ventricular end systolic diameter; LA:Ao, diameter of left atrium and aortic root ratio; FS, left ventricular fractional shortening; EF, left ventricular ejection fraction; VHS, vertebral heart score; BUN, blood urea nitrogen

Table 3 Clinical evaluation of dogs treated with ivabradine (IVA) and propranolol (Control) for 1 month

%Change	**15 Days**		**30 Days**	
	Control	**IVA**	**Control**	**IVA**
Echocardiography				
LVIDs (cm)	-10.27	-7.07	-11.63	0.76
LVIDd (cm)	-8.62	-14.86	-11.90	-3.81
LA:Ao	-3.89	-1.22	4.62	0.50
FS (%)	4.61	6.04	0.65	5.27
EF (%)	2.91	7.21	2.96	4.10
Blood pressure (mmHg)				
Systolic	-9.39	2.81	1.26	-6.37
Heart rate (bpm)	-21.67	-10.41	-14.0	-10.88
Radiographic				
VHS	-10.17	-3.79	-10.19	-11.93

Control group (n=7). Ivabradine group (n=6). LVIDd, left ventricular end diastolic diameter; LVIDs, left ventricular end systolic diameter; LA:Ao, left atrium and aorta ratio; FS, left ventricular fractional shortening; EF, left ventricular ejection fraction; VHS, vertebral heart score; BUN, blood urea nitrogen

Electrocardiographic findings: The rhythms of ECGs in the ivabradine-treated group at days 15 and 30 after treatment are shown in Figure 3. The heart rate decreased by 10% in the ivabradine group and decreased by 14% in the propranolol group at 30 days after treatment. In the ivabradine group (*n*=6), the cardiac rhythms in the ECG examination included sinus tachycardia in 4 dogs (67%) and respiratory sinus arrhythmias in 2 dogs (33%). In the control group (*n*=7), 4 dogs (57%) presented sinus tachycardia and 3 dogs had premature supraventricular beats (43%).

Echocardiographic findings: Results are shown in Table 3. Examples of M-mode echocardiographic images from each group are shown in Figure 4. After 15 days of treatment, the end diastolic measurements of left ventricular diameter in the control and ivabrabine groups decreased by 8.26% and 14.86%, respectively. The IVSd, IVSs, LVPWs and LVPWd were not different after ivabradine treatment. Decrease in the LA/AO ratio measured during the mid-diastole was observed in both groups. Non-significant improvements in ventricular function such as left ventricular EF were observed until 30 days after ivabradine treatment.

Quality of life: Scores of life quality from the questionnaires of both groups were calculated for each question (Table 1). Improvements, but not statistically significant, in the quality of life scores (Fig 5) were observed until 30 days after ivabradine treatment.

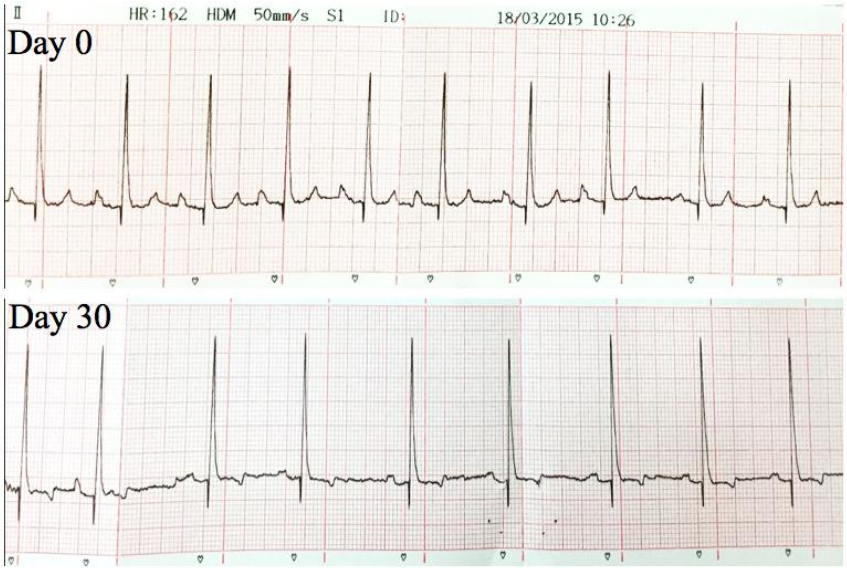


Figure 3 Electrocardiography of ivabradine-treated group at day 0 and day 30 after treatment

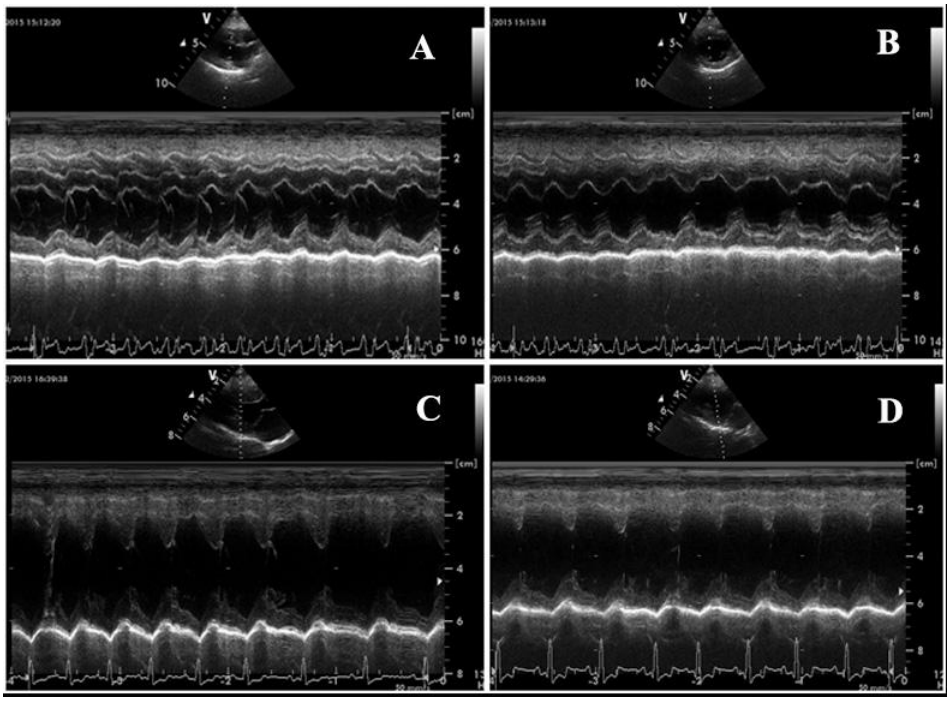


Figure 4 M-mode echocardiographic images of dogs in control group at day 0 (A) and day 30 (B), and ivabradine-treated group at day 0 (C) and day 30 (D)

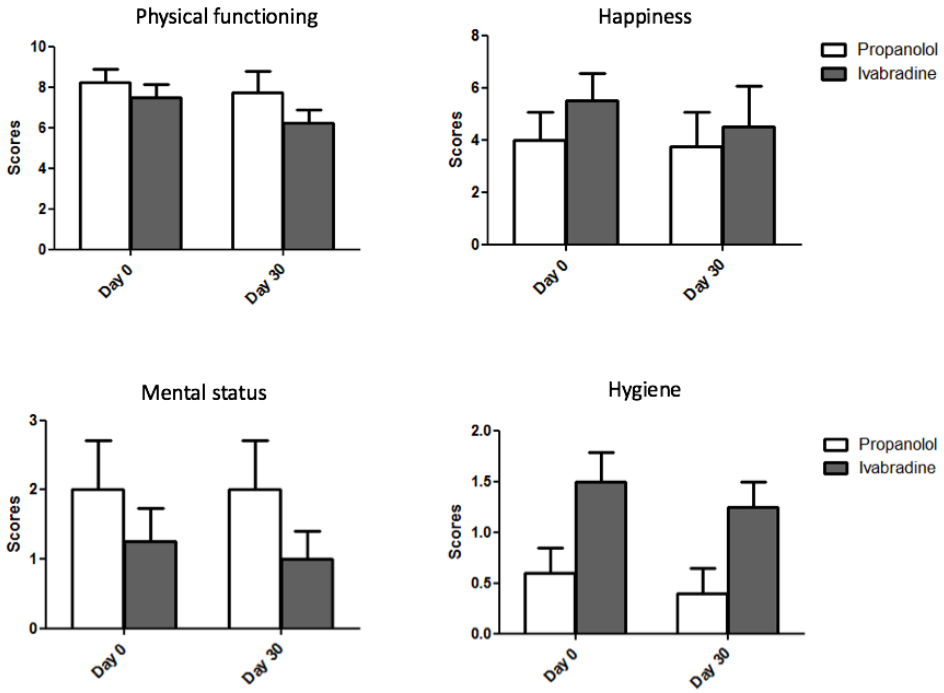


Figure 5 Analysis of scores of life quality. Dogs that received propranolol and ivabradine showed lower scores than the baseline, indicating improvement in life quality.

Discussion

Non-selective beta-adrenergic blockers such as propranolol have been used as medications for heart failure treatment. Ivabradine is a new heart rate lowering therapeutic option for congestive heart failure. However, the ideal dose of ivabradine for dogs with congestive heart failure is unknown. In this study, the oral dose of 0.5 mg/kg twice a day and subsequently of 0.3 mg/kg twice a day were chosen according to Hani et al. (2009) to better understand the effect of ivabradine in congestive heart failure dogs. When comparing the heart rate lowering effects, the faster at onset but not long-lasting was observed in the propranolol treatment group, which may be associated with their pharmacodynamics profiles. Another factor that is presumed to influence the efficacy of treatment is baseline of heart rate. A previous study by Bohm et al. (2010) showed that the effects of ivabradine on heart rate were significantly related to baseline heart rate, but not to beta-blocking agents. Therefore, baseline heart rate might influence the treatment efficacy between the groups. The limitation of this study was the short duration of treatment (30 days); ivabradine was not able to improve the ventricular volume in dogs with congestive heart failure stage C as compared with propranolol. Future studies should be performed with long-term treatment in order to investigate ventricular remodeling response, which is affected by dose and time of treatment of at least 3 months generally. The dogs in ivabradine treatment group showed improvement, but not statistically significant, in heart function such as the left ventricular ejection fraction and life quality. Although the ivabradine-treated group did not significantly improve heart function and quality of life, it was considered that ivabradine could be beneficial to the treatment of dogs with congestive heart failure. Regarding hygiene, the basal hygiene score was lower in the control group than in the ivabradine-treated group. Under this circumstance, the quality of life score was answered by the owners, blinded to the medications, we cannot exclude some degree of subjectivity in the evaluation from questionnaire, and this is a limitation of this study. Due to the small number of dogs in our recent study, additional studies with a larger number of animals are needed to determine potential benefit of the treatment as well as ideal dose of the treatment. Moreover, future studies comparing effects of treatment with other anti-arrhythmic agents such as carvedilol versus ivabradine should be performed to make the most promising new treatment option for congestive heart failure dogs. Another limitation of this study was the short period of follow-ups. New studies should be performed with long-term follow-ups to better evaluate the treatment of ivabradine in heart failure dogs.

Conclusion

In conclusion, ivabradine at doses of 0.3 mg/kg can be used to maintain heart rate without affecting cardiac function. Our study provided initial evidences that ivabradine can be safely administered to dogs with congestive heart failure.

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บทคัดย่อ

การศึกษาประสิทธิภาพของยาไอวาบราดีนต่อการทำงานของหัวใจห้องล่างซ้าย ในสุนัขที่มีภาวะหัวใจล้มเหลว

ศจิกา สีงาม[1] สุนทรี เพ็ชรดี[2]

ปัจจุบันไอวาบราดีน **(Ivabradine)** เป็นยาสำคัญที่ใช้ในมาตรฐานการรักษาผู้ป่วยที่มีภาวะหัวใจล้มเหลว และอาจนำมาใช้ประโยชน์ในการรักษาสุนัขที่มีภาวะหัวใจล้มเหลวเช่นกัน ยาไอวาบราดีน **(I_f Channel inhibitor)** เป็นยาทางเลือกใหม่ที่มีผลในการลดการทำงานของเซลล์ที่มีหน้าที่ควบคุมจังหวะการเต้นของหัวใจ และลดอัตราการเต้นของหัวใจ ปัจจุบันเริ่มมีการนำยาไอวาบราดีนมาใช้ในการทดลองในสุนัข เพื่อศึกษาประสิทธิภาพของยาเพิ่มมากขึ้น แต่ยังไม่มีรายงานการใช้ไอวาบราดีนในการรักษาสุนัขที่มีภาวะหัวใจล้มเหลว ดังนั้น การศึกษาครั้งนี้จึงศึกษาผลของยาไอวาบราดีนต่อการทำงานของหัวใจห้องล่างซ้ายในสุนัขที่มีภาวะหัวใจล้มเหลว **โดย**ทดลองในสุนัขที่มีภาวะการทำงานของหัวใจล้มเหลวจำนวน **13** ตัว ออกเป็น **2** กลุ่ม ได้แก่ **(i)** กลุ่มควบคุม **active** ได้รับยา **propranolol** ขนาด 0.5 มก./กก. และ **(ii)** กลุ่มที่ได้รับยาไอวาบราดีนขนาดเริ่มต้นที่ 0.5 มก./กก. วันละ **2** ครั้ง นาน **7** วัน และคงที่ที่ขนาด **0.3** มก./กก. วันละ **2** ครั้ง จากนั้นใช้การตรวจคลื่นไฟฟ้าหัวใจในการประเมินชนิดของการเกิดภาวะหัวใจเต้นผิดจังหวะ ความดันโลหิต และ ประเมินการทำงานของหัวใจด้วยเครื่องตรวจหัวใจชนิดคลื่นเสียงความถี่สูง ก่อนได้รับยา และ 15 และ 30 วันหลังได้รับยา ผลการศึกษาพบว่ายาไอวาบราดีนสามารถลดอัตราการเต้นของหัวใจ และทำให้คุณภาพชีวิตของสุนัขดีขึ้นหลังได้รับยา นอกจากนี้ ยังพบว่า **ejection fraction** และขนาดของหัวใจห้องล่างซ้ายไม่มีการเปลี่ยนแปลง ผลการทดลองนี้แสดงให้เห็นว่า ยาไอวาบราดีนสามารถลดอัตราการเต้นของหัวใจ และทำให้คุณภาพชีวิตของสุนัขที่มีภาวะหัวใจล้มเหลวดีขึ้น โดยไม่มีผลข้างเคียงที่ไม่พึงประสงค์

คำสำคัญ: ไอวาบราดีน ยาต้านการเต้นผิดจังหวะของหัวใจ ภาวะหัวใจล้มเหลว การทำงานของหัวใจ สุนัข

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