J Vet Clin 29(3) : 203-206 (2012)

Journal of Veterinary Clinics
www.ksvc.or.kr

Evaluation of Diuretic and Hemodynamic Effect of Extract from *Akebia quinata Decaisne* in Dogs

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(Accepted: June 12, 2012)

Abstract : Treatment for heart failure is directed to reduce atrial volume overload by diuretic agents, to lessen ventricular pressure overload by vasodilatory agents and to increase myocardial performance through inotropic agents. Of those cardiac therapeutics, diuretic agents are the most important to control heart failure in dogs, although long-term use often causes detrimental side-effects such as acute renal failure and electrolyte abnormalities. Thus, this study was designed to find a new diuretic agent from medicinal herbs which has better diuretic effect and less unfavorable complications in dogs. In a preliminary study performed with 5 normal healthy dogs, the extract from *Akebia quinata Decaisne* showed mild to moderate diuretic effect (0.3-0.5 potency of furosemide 2 mg/kg) and minimal changes in serum chemistry and electrolyte. Although the study population was not large enough and study period was not sufficient enough, this study found a good alternative diuretic agent which can replace or reduce the use of furosemide in dogs with heart failure.

Key words **:** diuretics, *Akebia quinata Decaisne,* heart failure, CMVI, dogs.

Introduction

Diuretics are the first line therapy in the management of heart failure (HF). In progressed HF, the blood volume is increased to maintain cardiac output (CO) and blood pressure (BP). But this increase causes elevation of left atrial pressure (LAP) and left ventricular filling pressure (LVFP). Elevated LAP causes pulmonary edema that can lead to cough, dyspnea, and even death. Elevated LVFP causes left ventricular dilatation, eccentric hypertrophy and increase cardiac work load, oxygen demand of myocyte. To manage this edematous condition and improve symptoms, diuretic therapy is essential. In the congested condition with CHF, diuretics are extremely effective in relieving symptoms, reducing intracardiac pressures, and improving cardiac performance (1,6). In veterinary medicine three classes of diuretics are used clinically to treat HF: thiazide diuretics, aldosterone antagonists, loop diuretics.

Diuretic therapy using those drugs has the potential to cause undesirable effects, primarily electrolyte disturbances, dehydration and prerenal and renal azotemia. Furthermore, long term diuretic therapy in HF induces diuretic resistance which is the clinical state in situation when diuretic response is diminished or lost (2). Therefore there is demand for a new diuretic agent which can minimize the side-effect and resistance in dogs with heart failure.

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Akebia quinata Decaisne (AQD, Korean name: eu-rum) is a native plant that grows widely in China, Japan and Korea. The fruits and stem of AQD have been used in oriental medicine to treat urinary tract inflammatory disease, edema, prostatitis, obesity, urinary incontinence, dysuria. It is also used for promoting diuresis and blood circulation in traditional Chinese folk medicine (7). There are some studies that demonstrated the effect of AQD extract to the renal function and its diuretic effect. One study reported that *Akebiae caulis* extract increases renal blood flow and glomerular filtration rate in the acute renal failure induced by repeated injections of gentamicin sulfate in rats (4). And *Akebia Lignum* EtOH extract, when given intravenously, produced a fall in blood pressure in rabbits (3). The large amount of potassium salts in the *Akebia caulis,* approximately 30%, is thought to be the cause of diuretic action but its exact mechanism is unknown.

The aim of this study is to identify the effect of AQD on diuresis and hemodynamics by comparing with furosemide.

Materials and Methods

Animals

Five normal healthy dog (3 males and 2 females) weighing between 1.5 and 4.8 kg of body weight (3.13 ± 1.38) were enrolled in this study. All animals were considered healthy based on physical examination, complete blood count and plasma biochemistry. All dogs were housed individually in cages. The dogs were fed commercial dry food twice daily and had free access to water. This study was carried out at

the Kangwon National University Veterinary Medical Teaching Hospital and was approved by the Institutional Animal Care and Use Committee.

Study design

Two separate cross-over designs were used for the study. In the first study, the dogs were administered AQD extracts at a dose of 17.44 mg/m^2 of body surface area orally, three times a day for 6 days. And then in the second study, the dogs received furosemide at a dose of 2 mg/kg orally, twice a day for 6 days. The wash out period was 14 days between two studies. Urine was collected for 3 days prior to first study to determine pre-treatment values. For accurate urine collection the bladder was completely emptied by catheterization just before the beginning of the collection period and the Foley Balloon Catheter (Sewoon Medical co., Ltd.) remained placed in the bladder during the study period. The urine was collected through closed-system bag over a 12 hour period and its volume measured. Daily water consumption was also recorded throughout the study period. Blood and urine samples were collected on the first day of each study to provide baseline data. On the 1st and 6th days of each study, blood and urine samples were collected and body weight, blood pressure, heart rate were measured. The blood and urine samples were immediately analyzed.

Urine and plasma assay

Blood samples were collected from the jugular vein into a tube containing heparin for plasma biochemical analyses and into tubes containing EDTA for hematological analyses. They were immediately tested right after collection. The plasma protein, BUN, CRE concentrations (mg/dL) were measured by use of an autoanalyzer (Vetscan VS2, ABAXIS, USA). The plasma sodium, potassium, and chloride (mEq/L) concentrations were measured by use of electrolyte analyzer (Rapidchem, Bayer HealthCare, Germmany). The urine output (mL/kg/h), 24-hour urine volume, and urine specific gravity (USG) were immediately measured after collection. The endogenous creatinine clearance was calculated by use of a standard formula as follows: Creatinine clearance (mL/kg/min) = (urine creatinine [mg/dL] × urine volume [mL/kg/min]) / plasma creatinine (mg/dL)

Preparation of extracts of *Akebia quinata Decaisne*

The extract was prepared according to the traditional method used in Korea as a decoction as follows: 3 kg of AQD was boiled at 100°C in 21 L of water for 5 hours and then cooled to room temperature. The remaining volume of aqueous *Akebia* extration was 12 ml. The concentration of AQD in the extract was approximately 0.25 mg/ml. The administration dosage of AQD extract was determined based on earlier study (Lee *et al*., 1978). Administration dose per kg was converted into dose per body surface area. *Akebia* extraction is administrated at a dosage of 17.44 mg/m^2 of body surface area 3 times a day.

Assessment of potential adverse effects

Any side effects from extract of AQD treatment including gastrointestinal signs (e.g. vomiting, diarrhea, anorexia), abnormal behavior (e.g. lethargy, confusion, uneasiness), neurological signs (e.g. seizure), and electrocardiological signs (e.g. QT prolongation, PR prolongation) were evaluated. Plasma protein, CRE, BUN, ALP concentration and PCV were evaluated.

Statistical Analysis

Results are expressed as mean ± SD. In the preliminary study, 1-way ANOVA was used to analyze the 24-hour urine volume and 24-hour urinary sodium and potassium excretions among treatments. The differences in plasma BUN, CRE, and

Table 1. Effects of administration of AQD extract and furosemide (2 mg/kg) for urine volume, daily water consumption, urine BUN, CRE and urine specific gravity (expressed as mean ± SD)

Parameters	Pre-treatment	AQD extract	Furosemide
UVd (ml/24h)	60 ± 33.59	88 ± 30.41*	124 ± 39.42**
UVm (ml/kg/min)	0.19 ± 0.16	0.20 ± 0.17	0.23 ± 0.19
WC (ml/24h)	150.84 ± 28.81	168.25 ± 32.31	222 ± 30.22
UBUN (mg/dL)	132 ± 18.25	116.67 ± 94.87*	77.67 ± 43.82*
UCRE (mg/dL)	7.17 ± 3.270	6.9 ± 4.44	4.37 ± 3.41*
C_{cr} (mL/kg/min)	1.36 ± 0.567	1.4 ± 0.78	1.21 ± 0.63*
UNA^+ (mmol/L)	30.63 ± 18.18	48.03 ± 18.13	51.67 ± 24.62*
UK^+ (mmol/L)	137.29 ± 83.00	176.03 ± 28.86*	68.06 ± 15.88*
UCl^- (mmol/L)	134.60 ± 67.06	171.93 ± 32.29	101.63 ± 9.07
pH	7.33 ± 1.53	6 ± 1	7.33 ± 0.5
USG	1.4 ± 0.01	1.03 ± 0.01	1.02 ± 0.01

UVd = daily urine volume, UVd = urine production per minute, WC = daily water consumption, UBUN = urine BUN concentration, UCRE = urine CRE concentration, C_{cr} = endogenous creatinine, UNA^+ = urine NA^+ concentration, UK^+ = urine K^+ concentration, UCl^- = urine Cl^- concentration, USG = Urine specific gravity, *= $P < 0.05$, **= $P < 0.001$

electrolyte concentrations at baseline and after treatment were analyzed by use of a paired *t* test. A value of $P < 0.05$ was considered significant. All statistical analyses were performed by use of statistical computer software (SAS, USA).

Results

Urine volume

Compared pre-treatment group, ADQ extract group induced significant increase in the daily urine volume (Table 1, $P < 0.05$). Furosemide treatment also induced significant increase in the daily urine volume compared control ($P < 0.05$) and AQD extract administration (Table 1, $P < 0.05$). Urine concentration of K^+ and Na^+ was markedly increased in AQD extract group compared with pre-treatment group (Table 1). AQD extract administration induced increase in creatinine clearance compared with pre-treatment group but in furosemide group creatinine clearance was decreased compared with pre-treatment group (Table 1).

Heart Rate, Blood Pressure, Body weight

Heart rate was decreased in AQD extract group compared with pre-treatment group and blood pressure was also decreased. In furosemide group heart rate was increased but blood pressure was decreased compared with pre-treatment group (Table 2). Those changes were statistically significant ($P < 0.05$). Body weight was decreased in AQD extract group and furosemide group compared with pre-treatmemt group. However this change was not statistically significant ($P > 0.05$).

Table 2. Effects of administration of AQD extract and furosemide (2 mg/kg) for heart rate, systolic blood pressure and body weight (expressed as mean ± SD). *= $P < 0.05$

Parameters	Pre-treatment	AQD extract	Furosemide
Heart rate (beats/min)	143 ± 15	140 ± 14	149 ± 21
Systolic blood pressure (mmHg)	169 ± 20	154 ± 17*	143 ± 13*
Body weight (kg)	3.13 ± 1.4	3.4 ± 1.6	3.0 ± 1.2

Table 3. Clinicopathologic variables; packed cell volume (PCV), plasma alkaline phosphate (ALP), albumin (ALB), total protein (TP), blood urea(BUN), creatinine (CRE), plasma electrolyte. *= $P < 0.05$

Parameter	Pre-treatment	AQD extract	Furosemide
ALP	255.25 ± 87.18	156.75 ± 85.82	177.6 ± 109.95
ALB	3.2 ± 0.45	3.1 ± 0.39	3.2 ± 0.31
TP	6.32 ± 0.12	5.85 ± 0.25	6.12 ± 0.37
BUN	21.5 ± 7.33	25.75 ± 5.19	32.67* ± 19.22
CRE	1.0 ± 0.26	0.98 ± 0.39	0.83 ± 0.42
Na^+	140.13 ± 0.91	140.30 ± 2.25	140.43 ± 6.52
K^+	114.33 ± 2.38	4.5 ± 0.17	4.5 ± 0.17
Cl^-	114.33 ± 2.38	115.77 ± 0.12	114.97 ± 4.46
PCV	46.45 ± 5.30	41.575 ± 2.97	41.6 ± 11.9

Assessment of side-effects

USG was decreased in administration of AQD extract and furosemide compared with pre-treatment. Furosemide administration induced lower USG than AQD extract administration (Table 1). Serum electrolyte was not statistically significantly changed in administration of AQD extract and furosemide (Table 3; $P > 0.05$). Serum BUN level was significantly increased in furosemide administration compared with pre-treatment ($P < 0.05$) but creatinine levels were unchanged (Table 3; $P > 0.05$).

Discussion

Major problems of diuretic therapy in dogs are that it can cause hypovolemia, electrolyte imbalance (especially hypokalemia) and acid-base imbalance (particularly metabolic alkalosis) which may reduce the contractile performance of the heart and contribute to arrhythmias. Also it can induce elevation of the rennin-angiotensin-aldosterone system (RAAS) in dogs with heart failure, which can cause peripheral vasoconstriction, myocardial fibrosis and volume retention. Those effects can deteriorate heart failure faster. Therefore finding new diuretic agents, which have less side effects and are more efficacious, is very important in veterinary medicine, although large scale clinical trials of diuretic agents on dogs have rarely been done. Thus, this study was designed to find a new diuretic agent (*Akebia quinata Decaisne)* from medical herbs which has better diuretic effect and less unfavorable complications in dogs.

Two studies have evaluated the diuretic effect of this herb Kim *et al* (4) found the extract from this herb could increase glomerular filtration rate (GFR) and renal blood flow (RBF), whereas Lee *et al* (5) found the extract could decrease GFR and RBF. However, in this study, we found that all the dogs who had this extract showed an increased diuretic effect, meaning the elevation of GFR and RBF in dogs. Our study result was opposite of this previous study (5). It is probably because the amount given in our study was 8 times higher (8 mg/m^2 of body condition score) so that our study dogs might show dose-dependent diuretic effect, although this effect was only 1/3 potency of furosemide.

Interestingly, in dogs having AQD extract, heart rate was decreased and blood pressure was also decreased. In contrast, in dogs with furosemide, heart rate was increased but blood pressure was decreased. Lowering effect of heart rate in AQD extract will be beneficial for long-term management in dogs with severe heart failure, because it helps to reduce risk of tachyarrhythmias and to improve diastolic function of ventricles. We are not sure why heart rate is reduced in dogs having AQD extract, because there has been no study evaluating hemodynamic effect of AQD, to date. However we suspected that AQD extract may either/both decrease sympathetic tone

or/and increase vagal tone in dogs, and thus heart rate is decreased. Further study is warranted to reveal the effect on autonomic nervous tone by AQD extract.

No dog showed particular adverse effects from AQD extract during the test period. Plasma creatinine, BUN, ALP and total protein concentration was unchanged, although azotemia was noticed in dogs with furosemide. PCV also was unchanged during administration of AQD extract. Serum electrolyte levels showed no significant changes after the administration of AQD extract. This result suggests that the AQD extract can be a good alternative or subsidiary diuretic agent which has minimal side effect on renal function and serum electrolyte in dogs.

Our study limitations were that i) the study period was too short to evaluate long-term therapeutic and adverse effects in dogs treated with this extract, ii) this study was not a clinical trial so that we could not evaluate whether these extract might be truly effective in dogs heart failure and might lengthen survival period after treatment. Therefore the long-term and more controlled study is required to clarify these study limitations.

In conclusion, this study provides clear evidence that the extract from AQD has potentially beneficial therapeutic effects in dogs with heart failure (e.g. increasing diuresis and decreasing heart rate), without particular adverse effects.

Acknowledgement

This study was supported by research grants from the Korea Sanhak Foundation and the Institute of Veterinary Science (KNU).

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개에서 목통(*Akebia quinata Decaisne*) 추출물의 이뇨효과 평가

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요 약 : 심부전의 치료는 심방의 용적 과부하를 줄이기 위한 이뇨제, 심실 압력 과부하를 줄이기 위한 혈관확장제, 심근의 수축력을 향상시키기 위한 강심제 치료로 이루어진다. 이 중 이뇨제가 개의 심부전 조절에서 가장 중요하다. 하지만 장기간의 이뇨제 사용으로 급성 신부전이나 전해질 이상과 같은 부작용이 발생할 수 있다. 따라서 이 연구는 개에서 부작용이 적으면서 더 나은 이뇨효과를 가지는 생약성분의 이뇨제를 찾기 위해 설계되었다. 5마리의 건강한 개를 대상으로 한 예비실험에서 목통(*Akebia quinata Decaisne*) 추출물은 경도에서 중등도의 이뇨효과(furosemide 2 mg/kg 용량 효과의 0.3-0.5배의 효력)를 보였으며 혈청화학 수치와 전해질 변동은 거의 없었다. 실험 개체 수가 적고 기간이 충분하지 않지만 이 실험을 통해 심부전 환자에서 furosemide의 사용량을 줄이거나 대체할 수 있는 생약성분의 이뇨제 성분을 발굴하였다.

주요어 : 이뇨제, 목통, *Akebia quinata Decaisne,* 심부전, 개