J Vet Clin 29(6) : 435-440 (2012)

Journal of Veterinary Clinics
www.ksvc.or.kr

Evaluation of Therapeutic Effect of the Extract from Rhubarb (*Rheum officinalis*) in Dogs with Chronic Renal Failure

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(Accepted: November 12, 2012)

Abstract : This study was designed to evaluate the clinical efficacy and safety of Rhubarb extracts (Rubenal®) in dogs with chronic renal failure (CRF). Client-owned 40 dogs with CRF graded International renal interest Society (IRIS) II-III were enrolled in this study. The dogs were equally allocated and blindly administered with Rubenal® or placebo. The following items were evaluated at day 0, 30, 90 and 180: body condition score (BCS), clinical score (appetite, polydipsia/polyuria, quality of life score), hemogram (WBC, RBC, PCV), serum biochemistry (ALT/AST, ALP, Creatinine/BUN, total protein, albumin), serum electrolyte (Na, K, Cl, Ca, P), systolic blood pressure, urinalysis (UPC, USG) and IRIS stage. In this study, we found that the Rubenal® preparation was well tolerated by dogs and induced no adverse effects. Statistically significant improvements were observed in clinical score (quality of life score by vet and clients), serum BUN and creatinine levels, serum phosphorus concentration, level of proteinuria, and the IRIS score of CRF in dogs after 6 month of treatment of Rubenal®. Those findings suggested that the Rhubarb extracts can improve the clinical signs of CRF (i.e. azotemia, hypertension, proteinuria, hyperphosphoremia) and the quality of life (i.e. BCS, clinical score) and can retard the progression of CRF in dogs. Therefore the Rhubarb extracts can be a good supplementary drug for treating dogs with subclinical and clinical renal diseases. However, care should be taken for interpreting our result, because this study is not double-blinded controlled study but pilot study.

Key words **:** Rhubarb extracts, *Rheum officinalis,* CRF, chronic kidney disease.

Introduction

Chronic renal failure (CRF) is the progressive and irreversible loss of secretory and excretory function due to the destruction of nephrons (2). CRF can manifest itself due to the action of a factor or factors, damaging every part of the nephron functional units of the kidney in dogs and cats. The majority of CRF cases reported in dogs (66%) were due to chronic interstitial nephritis, with chronic glomerulonephritis (28%) and renal amyloidosis (6%) accounting for the remaining cases. Since the cause of CRF can not be easily defined in most cases and the most CRF cases are slowly progressed to the decompensation stage (2), the therapeutic aims should be focused on either stopping or retarding the development of the pathological changes that are beginning to appear.

Pharmacological interventions such as anti-hypertensive, anti-inflammatory and anti-hyperlipidemia drugs, including dietary approaches, have all proved beneficial in the treatment of CRF (16). However, an appreciation of the mechanisms behind the development and maintenance of the chronic inflammatory process, prompted studies that focused on elucidating the pathogenesis of the disease, and halting the consequential renal fibrosis that arises in response to the chronic development of CRF (8,9,15).

Plant extracts and bioactive molecules have been utilized extensively in many areas of medicine (7). Rhubarb extract (*Rheum officinalis*) is an example of a plant extract whose bioactive properties have been studied extensively for many years (12,13). Animal studies found that rhubarb extract inhibited the proliferation of renal tubule cells in rats and delayed the development of renal glomerular fibrosis, although this inhibition was dependent on the dose and time of administration (4,17). Therefore, this study focused on elucidating the clinical efficacy and safety of a commercially available Rhubarb extract (i.e. Rubenal® preparation), for treating dogs with chronic renal failure.

Materials and Methods

Study Population

Two groups of dogs (from Kangwon National University Veterinary Medical Teaching Hospital and alliance local veterinary clinics) having IRIS stage II-III CRF was enrolled in this study. The dogs were selected for the study on the basis of their clinical CRF symptoms, a serum creatinine concentration ≥ 1.4 mg/dl and the presence of albuminuria (with a

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urinary albumin to creatinine ratio > 1). Each group of dogs was allocated into a Rubenal group and a placebo group. All dogs were free of other systemic diseases revealed by routine clinical exam and laboratory tests. Rubenal group (20 dogs aged between 5-14 years old) weighing between 1.5 and 7.8 kg of body weight (4.5 ± 1.38 kg) were used, while the placebo (20 dogs aged between 7-13 years old) weighing between 2.1 and 8.7 kg of body weight (5.2 ± 3.1 kg) were used. The dogs were fed commercial renal prescription diet (Renal®, Royal Canin, France) 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. Prior to study, we obtained the consent from the owner for this study.

Assessment Criteria

The following criteria were evaluated after the administration of the extract of rhubarb (*Rheum officinalis*) for 6 months.

1. General Body condition score (BCS)
   · General condition (Body score: 1 = very lean, 2 = lean, 3 = normal, 4 = obese, 5 = very obese)
2. Clinical Score (Appetite, polyuria/polydipsia, QOL)
   · Appetite (2- normal, 1- reduced, 0- absent)
   · Polyuria (0- absent, 1- mild, 2- moderate, 3- severe) Severity was graded by daily volume of urination
   · Increased thirst (0- yes, 1- no) Severity was graded by daily consumption of water.
   · Quality of life (QOL) by Owner (3- marked improvement, 2- improvement, 1- minor improvement, 0- no improvement/worse) Graded by activity and food consumption
   · Quality of life (QOL) by veterinarian (3- marked improvement, 2- improvement, 1- minor improvement, 0- no improvement/worse). Graded by activity and food consumption
3. Hemogram (WBC, RBC, PCV)
4. Serum Biochemistry (ALT/AST, ALP, Creatinine/BUN, total protein, Albumin)
5. Serum Electrolyte (Na, K, Cl, Ca, P)
6. Systolic blood pressure (Doppler method, measured at the front limbs)
7. Urinalysis (Urine protein/creatinine ratio [UPC], urine specific gravity [USG])
8. International renal interest Society (IRIS) stage: Creatinine level in IRIS I (< 1.4 mg/dL), IRIS II (1.4-2.0 mg/dL), IRIS III (2.1-5.0 mg/dL), IRIS IV (> 5.0 mg/dL)

Preparation of the extract from *Rheum officinalis*

The extract from *Rheum officinalis* was commercially available as labeled as Rubenal®(Vetoquinol, France). This medication was used in this study. The medication was administered in a dose of 15 mg/kg daily for 6 months in dogs enrolled in this study.

Study design

The extract from *Rheum officinalis* was administered to Rubenal group, while the multi-vitamin tablet (Canivita, Lee Hyun, Korea) was administered to the placebo group. The owners and veterinarians did not know which medication was administered to their dogs (blindly and randomly allocated). Clinical examinations and collection of blood for testing, as well as the urinalysis and blood pressure measurements were performed 4 times according to the following pattern:

D0- on the day of selection for the studies (study 1)
D30- after 1 month (study 2)
D90- after 3 months (study 3)
D180- after 6 months (study 4).

The clinical assessment variables included the parameters mentioned above, scored on a points scale:

Statistical Analysis

Results are expressed as mean ± SD. The differences in clinical assessment variables between the Rubenal and placebo groups 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

Signalment of study population

In placebo group of dogs, 11 male dogs and 9 female dogs were included. The mean age was 8.3 ± 3.4 yr. The CRF stage in 10 dogs was IRIS II whereas that of the rest 10 dogs was IRIS III. In Rubenal group of dogs, 9 male dogs and 11 female dogs were included. The mean age was 7.4 ± 4.2 yr.

Assessment of general condition and clinical score

The mean body condition score was moderately decreased from 3.5 ± 0.3 to 2.8 ± 0.8 after 6 months of treatment in the

Table 1. Changes in body condition score and clinical score after administration of Rubenal® for 6 months

		D0	D30	D90	D180
BCS	Placebo	3.5 ± 0.3	3.2 ± 0.5	3.0 ± 0.7	2.8 ± 0.8
	Rubenal	3.4 ± 0.2	3.3 ± 0.4	3.4 ± 0.4	3.2 ± 0.3*
Appetite	Placebo	1.5 ± 0.2	1.4 ± 0.3	1 ± 0.4	0.8 ± 0.1
	Rubenal	1.8 ± 0.2	1.4 ± 0.4	1.4 ± 0.4	1.8 ± 0.3
PD/PU	Placebo	1.5 ± 0.5	1.2 ± 0.8	1.0 ± 1.0	0.8 ± 1.2
	Rubenal	1.5 ± 0.5	1.5 ± 0.5	1.2 ± 0.8	1.3 ± 0.7
QOL by vet	Placebo		1 ± 0.5	0.8 ± 0.3	0.4 ± 0.3
	Rubenal		1.5 ± 0.3	1.8 ± 0.4*	1.5 ± 0.3*
QOL by Client	Placebo		0.6 ± 1	0.7 ± 0.3	0.4 ± 0.5
	Rubenal		2 ± 0.5*	2.1 ± 0.3*	1.9 ± 0.3*

*. $P < 0.05$
QOL: quality of life, PD/PU: polydipsia/polyuria

placebo group, whereas the score did not change much in the Rubenal group (Table 1). The reduction of the BCS was significantly different between the two groups. The mean quality of life (QOL) scores judged by vets and clients significantly improved in the Rubenal group from one month after treatment. Those improvements were statistically significantly different between the two groups (Table 1). The appetite and the signs of PD/PU also improved in the Rubenal group after treatment with time (Table 1).

Assessment of hemogram, serum biochemistry and electrolytes

Although there was mild improvement in total number of RBC and PCV in the Rubenal group after treatment, this improvement was not statistically significant compared to the placebo group (Table 2). There was no change in the total number of WBC, despite treatment with Rubenal.

Although the mean concentrations of BUN and creatinine were increased in both groups with time, the level of elevation was more severe in the placebo group (Table 2). Furthermore, the mean concentrations of BUN and creatinine were significantly different in the blood samples taken at 180 days after treatment (Table 2). Although there were no changes in the serum total protein in both groups after treatment, the mean concentration of albumin was significantly higher in the Rubenal group (Table 2). There was no significant difference in hepatic enzymes between both groups after treatment (Table 2).

Table 2. Changes in hemogram, serum biochemistry and electrolytes after administration of Rubenal® for 6 months

		Reference	D0	D30	D90	D180
WBC (K/uL)	Placebo	6-17	13.6 ± 3.2	14.1 ± 4.3	12.4 ± 2.4	11.8 ± 3.1
	Rubenal		11.8 ± 2.2	12.4 ± 1.4	11.4 ± 1.4	13.8 ± 2.3
RBC (10E6/uL)	Placebo	5.5-7.5	5.5 ± 1.2	5.3 ± 1.5	4.5 ± 2.1	4.2 ± 0.8
	Rubenal		4.9 ± 1.3	5.1 ± 1.8	5.5 ± 0.4	4.8 ± 1.1
PCV (%)	Placebo		45 ± 12	37 ± 8	33 ± 13	31 ± 14
	Rubenal	37-55	47 ± 17	42 ± 9	37 ± 21	38 ± 11
BUN (mg/dL)	Placebo	7-25	45 ± 12	57 ± 23	65 ± 12	78 ± 31
	Rubenal		38 ± 8	45 ± 12	43 ± 25	52 ± 13*
Creatinine (mg/dL)	Placebo	0.3-1.4	2.8 ± 1.1	3.2 ± 0.5	3.4 ± 1.3	4.5 ± 2.1
	Rubenal		2.6 ± 0.8	2.8 ± 1.2	2.8 ± 1.5	3.2 ± 0.7*
ALT (U/L)	Placebo	10-118	78.3 ± 21.9	81.8 ± 32.1	82.7 ± 23.2	73.1 ± 29.5
	Rubenal		115 ± 14.6	111.0 ± 32.2	128.0 ± 21.0	124 ± 41.2
AST (U/L)	Placebo	16-50	31.9 ± 6.5	31.8 ± 5.3	30.2 ± 5.9	32.4 ± 6.5
	Rubenal		49.0 ± 5.1	43.1 ± 3.5	45.3 ± 7.9	43.2 ± 6.7
ALP (U/L)	Placebo	20-150	255.2 ± 87.1	156.7 ± 85.3	177.7 ± 109.9	213.8 ± 81.3
	Rubenal		162.3 ± 33.7	159.3 ± 53.4	173.4 ± 73.6	166.3 ± 45.2
TP (mg/dL)	Placebo	5.4-8.2	7.1 ± 0.41	7.2 ± 0.89	7.2 ± 0.88	7.3 ± 0.72
	Rubenal		7.6 ± 0.55	7.2 ± 0.11	7.6 ± 0.77	7.4 ± 0.35
ALB (mg/dL)	Placebo	2.5-4.4	3.7 ± 0.69	2.9 ± 0.17	2.9 ± 0.56	2.4 ± 0.37
	Rubenal		3.8 ± 0.59	3.7 ± 0.06	3.2 ± 0.62	3.1 ± 0.72
Na (mEq/L)	Placebo	138-160	140.1 ± 2.38	139.7 ± 1.91	138.7 ± 1.18	137.8 ± 2.11
	Rubenal		139.7 ± 1.57	139.8 ± 2.38	140.1 ± 2.02	140.3 ± 1.65
K (mEq/L)	Placebo	3.7-5.8	4.8 ± 0.42	4.8 ± 0.71	4.9 ± 0.32	5.2 ± 0.63
	Rubenal		4.6 ± 0.46	4.7 ± 0.05	4.4 ± 0.12	4.4 ± 0.58
Cl (mEq/L)	Placebo	100-120	114.3 ± 2.3	117.8 ± 3.1	109.4 ± 4.7	112.3 ± 5.1
	Rubenal		118.2 ± 1.57	115.7 ± 2.8	119.6 ± 3.2	113.2 ± 6.2
Ca (mg/dL)	Placebo	8.6-11.8	10.8 ± 0.38	10.1 ± 0.25	10.1 ± 0.84	10.2 ± 0.47
	Rubenal		10.2 ± 0.54	11.2 ± 0.27	10.7 ± 0.18	10.8 ± 0.25
P (mg/dL)	Placebo	2.9-6.6	6.28 ± 0.32	6.37 ± 0.64	6.81 ± 0.54	6.35 ± 0.72
	Rubenal		6.51 ± 0.53	7.24 ± 0.98	4.92 ± 0.73*	4.69 ± 0.42*

*. $P < 0.05$

WBC: white blood cells, RBC: red blood cells, PCV: packed cell volume, BUN: blood urea nitrogen, ALT: alanine transaminase, AST: asparate transaminase, ALP: alkaline phosphatase, TP: total protein, ALB: albumin, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, P: phosphorus

Table 3. Changes in systolic blood pressure, urine specific gravity (USG), urine protein creatinine ratio (UPC) and IRIS stage after administration of Rubenal® for 6 months

		Reference	D0	D30	D90	D180
SAP (mmHg)	Placebo	100-150	169 ± 16	172 ± 21	168 ± 13	171 ± 17
	Rubenal		168 ± 15	163 ± 14	166 ± 24	156 ± 16
USG	Placebo	1.015-1.050	1.011 ± 0.01	1.012 ± 0.01	1.011 ± 0.01	1.01 ± 0.01
	Rubenal		1.012 ± 0.01	1.014 ± 0.01	1.014 ± 0.01	1.012 ± 0.01
UPC	Placebo	< 0.5	1.4 ± 0.16	1.44 ± 0.08	1.44 ± 0.32	1.56 ± 0.28
	Rubenal		1.36 ± 0.12	1.32 ± 0.16	1.08 ± 0.16*	1.12 ± 0.24*
IRIS	Placebo	-	2.3 ± 0.5	2.4 ± 0.7	2.6 ± 0.4	3.1 ± 0.8
	Rubenal		2.5 ± 0.3	2.5 ± 0.6	2.4 ± 0.1	2.7 ± 0.3*

*. $P < 0.05$
SAP: systolic blood pressure, USG: urine specific gravity, UPC: urine protein: creatinine ratio, IRIS: international renal interest society

The mean concentration of phosphorus was gradually decreased in the Rubenal group with time after treatment. There was a significant difference in the concentration of phosphorus in the blood samples taken at Day90 and Day180 between the two groups (Table 2). The mean concentration of calcium was fluctuating but mildly increased in the Rubenal group after treatment. However, there was a significant difference in the concentration of calcium between the two groups after treatment (Table 2). There were no remarkable changes in the concentrations of sodium, chloride and potassium between both groups, despite 6 months of treatment (Table 2).

Assessment of systolic blood pressure, USG, UPC and progression of CRF

There was a mild reduction of the systolic blood pressure in the Rubenal group after treatment, where there was no change in the placebo group (Table 3). The ability of urine concentration in the Rubenal group was weakly preserved after treatment, although this ability was gradually lost in the placebo group (Table 3). The level of proteinuria was remarkably reduced in the Rubenal group with time, while there was no change in the level of proteinuria in the placebo group. The level of UPC was significantly different in the urine samples collected at Day 90 and 180 between the two groups (Table 3).

The overall IRIS score for the Rubenal group was not significantly different from the baseline (Day 0) to the end of the study (Day 180), although there was an insignificantly mild reduction of the IRIS score (Table 3) In contrast to the Rubenal group, the overall IRIS score for the placebo group was gradually increased (Table 3). The severity of chronic renal failure (CRF) was significantly different at the end of study (Day 180).

Discussion

Rhubarb extracts are popular herbs widely used in oriental medicine for the treatment of kidney diseases (10). Wang *et al* has proven the nephroprotective action of rhubarb extract by conducting a series of experiments in rats (10). Therefore, this study was designed to evaluate the clinical efficacy and safety of Rhubarb extract (Rubenal®) in dogs with chronic renal failure. We found that the Rubenal preparation was well tolerated by dogs and no adverse effects were observed. Despite differences in metabolism and tolerance among various animal species, including humans, the effect of rhubarb extract in dogs and humans has been found to be similar (1).

After 30 days of oral administration of rhubarb extract, clinical improvement was observed, including evident signs of a beneficial action on the kidney in cases of chronic insufficiency. Furthermore, we also observed decreased azotemia, which was associated with the improved general condition of the animals (appetite, BCS, QOL score, PD/PU). These results are in agreement with the observations of other study (13), who gathered data on the use of the rhubarb extract or compounds containing rhubarb extract in human subjects with CRF over a 10 year period. We evaluated the doses used, the duration of administration and the associated side effects of rhubarb, and found reduced azotemia and retarded progression of CRF. No adverse effects were observed, even in patients under long-term treatment with the rhubarb extract. The most significant effect with respect to CRF complications in dogs undergoing Rubenal treatment was the decreased serum phosphorus concentration. Hyperphosphatemia is one of the more significant symptoms of CRF related to the development of renal secondary hyperparathyroidism. After 6 months of treatment, serum phosphorus concentrations were significantly reduced from a mean value of 6.5 mg/dl to 4.7 mg/dl. The use of phosphorus-binding auxiliary preparations would have further reduced the apparent hyperphosphatemia, however, this was beyond the scope of this study.

Rhubarb extract also exhibits an antioxidant properties (12). This was found in the analysis of 55 botanical preparations, traditionally used in the treatment of urinary tract diseases. The highest antioxidant potentials were found in olive leaf extract, black cohosh extract (*Actaea racemosa*), rhubarb extract, liquorice and skullcap (*Scutellaria baicalensis*). The rhubarb extract contributes significantly to the protective

action when carrying out auxiliary procedures in urological patients. Rhubarb extract is still recommended in secondary kidney diseases such as renal complications due to diabetes. Yang and Li showed that the use of rhubarb in cases of experimentally-induced diabetes in rats prevented renal hypertrophy, and increased the glomerular filtration coefficient in the early stages of diabetic nephropathy (15). These observations are intriguing, given that in most cases of diabetes in dogs, any unfavorable outcome is attributed to CRF. The early implementation of auxiliary/nephroprotective treatment in dogs with newly diagnosed diabetes was found to either arrest or delay the onset of diabetic nephropathy. Antioxidant properties of rhubarb extract involve in retarding the progression of CRF, as noticed in this study. However, a recent human study found the efficacy of *Rheum officinale* in improving azotemia in patients with chronic kidney diseases is questionable (9), although *Rheum officinale* does not cause any serious side-effects.

In the pathogenesis of CRF, albuminuria plays a dual role, an indicator of renal glomeruli damage (3,6), and the risk of developing CRF (11). Moreover, hypertension and high proteinuria are correlated to the reduced life span in patients with CRF (11). Dogs receiving Rubenal® exhibited a steady reduction in the urinary protein/creatinine ratio (UPC), suggesting a reduction in albuminuria. In addition, group of dogs taking Rubenal exhibited a reduction of systolic blood pressure (reducing the risk of hypertension). The systolic blood pressure constituted an important prognostic indicator of survival time in dogs with CRF (11). A UPC ratio below 1 significantly lowers the risk of the animal developing uremia or even death (5).

In conclusion, our study suggested that the Rhubarb extract (Rubenal®) can improve the clinical signs of CRF (i.e. azotemia, hypertension, proteinuria, hyperphosphoremia) and the quality of life (i.e. body condition score, appetite and PD/PU) and can retard the progression of CRF in dogs. Therefore the Rhubarb extract can be a good supplementary drug for treating dogs with subclinical and clinical renal diseases. However, care should be taken for interpreting our result, because this study is not double-blinded controlled study. Also recent human study found the efficacy of *Rheum officinale* is limited for improving azotemia in patients with chronic kidney diseases. Therefore more controlled study should be conducted to prove the efficacy of the Rhubarb extract in dogs with CRF.

Acknowledgements

This study was supported from the Institute of Veterinary Science (KNU), Kangwon National University and Vetoquinol Korea.

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개의 만성 신부전에서 대황 추출물의 치료학적 효과의 평가

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요 약 : 이번 연구는 만성신부전이 있는 개에서 대황 추출물(Rubenal®)의 치료적 효과와 부작용을 평가하기 위해서 실시되었다. 보호자가 있는 만성신부전 IRIS II-III 단계의 개 40마리가 이번 연구에서 사용되었다. 개들에게 동일한 모양의 대황 추출물과 위약을 투여한 후 0, 30, 90, 180일 동안 관찰, 평가하였다: BSC, 임상적 평가(식욕, 다음/다뇨, QOL), 혈액 검사(WBC, RBC, PCV), 혈청화학검사(ALT/AST, ALP, Creatinine /BUN, Total protein, albumin), 전해질검사(Na, K, Cl, Ca, iCa, P), 혈압, 요검사(UPC, 요비중) 그리고 IRIS 단계를 평가하였다. 이번 연구에서 개들에게 대황 추출물을 적용하였을 때 부작용 없이 잘 받아들이는 것을 확인하였다. 또한, 통계학적으로 임상적 평가(수의사와 보호자의 QOL)와 혈청 BUN, creatinine 수치, 혈청 인 농도, 단백뇨의 양, 그리고 만성신부전의 IRIS 점수가 루비날 치료 6개월 후에 유의성 있게 개선되었다. 이러한 발견은 대황의 추출물은 만성신부적의 임상증상(i.e., azotemia, hypertension, proteinuria, hyperphosphoremia)과 삶의 질(i.e., body condition score, appetite and PD/PU)을 향상시키고, 개에서 만성신부전의 진행을 늦출 수 있다는 것을 보여준다. 그러므로 대황 추출물은 준임상적, 그리고 임상적으로 신장 질환을 치료하고 있는 개에게 좋은 보조제가 될 수 있다. 하지만 본 연구는 작은 규모의 파일럿 연구이므로 이중 맹검법의 대규모 실험을 통해 보다 정확한 실험결과의 재현이 요구된다.

주요어 : 대황 추출물, 루비날, *Rheum officinalis,* CRF, 만성 신부전