

The Effect of Chinese Rhubarb, *Rheum officinale*, with and without Benazepril on the Progression of Naturally Occurring Chronic Kidney Disease in Cats

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Background: Renal fibrosis is common in progressive kidney disease. Transforming growth factors β (TGF- β) are important mediators of all types of fibrosis, including renal fibrosis. Chinese rhubarb has been shown to have antifibrotic properties in part because of inhibition of TGF- β and has slowed the progression of kidney disease in rodent models.

Hypothesis: That administration of a Chinese rhubarb supplement will slow the progression of chronic kidney disease (CKD) in cats and the concurrent administration of Chinese rhubarb and benazepril will be more effective than either alone.

Animals: Twenty-nine client-owned cats with naturally occurring IRIS Stage 2 or early Stage 3 CKD and without comorbidity such as cancer, urinary tract obstruction, urinary tract infection, poorly controlled hyperthyroidism, or systemic hypertension were enrolled in the study.

Methods: A randomized, positive-controlled, prospective study was performed. Cats received Chinese rhubarb, benazepril, or both in addition to standard treatment for CKD. Repeated measures ANOVA was used to assess changes in serum creatinine concentration, body weight, hematocrit, urine protein: urine creatinine ratio (UPC), and systemic arterial blood pressure over time between and within treatment groups over an average of 22 months.

Results: No significant differences were detected in serum creatinine concentration, body weight, hematocrit, UPC, and systemic arterial pressure over time between or within treatment groups.

Conclusions and Clinical Importance: This study failed to detect a significant difference in the progression of CKD in cats treated with Chinese rhubarb, benazepril, or both. Further study in specific subsets of cats with CKD is warranted.

Key words: Cat; Chronic renal failure; Herb; Herbal; Rheum.

Chronic kidney disease (CKD) in cats is one of the most common causes of mortality in this species and prevalence of CKD increases with age.^{1,2} After the onset of azotemia, CKD often is progressive in cats and is thought to be self-perpetuating. Interstitial fibrosis and mononuclear inflammation are common histopathologic findings in feline CKD and there is evidence that advanced renal fibrosis is associated with the progression of CKD.^{3–6} Fibrosis may contribute to progressive disease by causing renal hypoxia, altering growth signals and cell survival, and leading to a maladaptive hyperdynamic state and proteinuria.^{7–11}

An underlying cause of renal disease rarely is found at the time of CKD diagnosis and therefore treatment usually employs renoprotective measures (eg, diet, enteric phosphate binders, angiotensin-converting enzyme inhibitors [ACEi]) designed to preserve renal function. Treatments that can slow the development of renal fibrosis potentially would be renoprotective and important. Transforming growth factors β (TGF- β)

Abbreviations:

ANOVA	analysis of variance
CBC	complete blood count
CKD	chronic kidney disease
IRIS	International Renal Interest Society
RAAS	renin-angiotensin-aldosterone system
TCC	transitional cell carcinoma
TGF- β	transforming growth factors β
TT4	total thyroxine
UPC	urine protein: urine creatinine

are upregulated in experimentally induced and naturally occurring fibrosis, including renal fibrosis.^{12–14} For this reason TGF- β , associated signaling cascades, and downstream mediators are the focus of much research related to renal fibrosis. Chinese rhubarb, *Rheum palmatum* and *Rheum officinale*, has been used for thousands of years to treat various diseases in traditional Chinese medicine. Chinese rhubarb and its constituents have been shown to have antifibrotic and anti-inflammatory effects *in vivo* and *in vitro* at least in part because of inhibition of TGF- β .^{15–18} In addition, in rodent models, rhubarb supplementation has decreased proteinuria and slowed progression of kidney disease.^{15,16} These effects appear to be synergistic with concurrent renin-angiotensin-aldosterone system blockade.^{15,17} The purpose of this study was to investigate the effects of a Chinese rhubarb supplement^a on the progression of naturally occurring CKD in cats. Our hypothesis was that a Chinese rhubarb supplement would slow the progression of CKD in cats and a Chinese rhubarb supplement and benazepril together would be more effective than either alone.

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Materials and Methods

Cats

Cats were recruited from the Kansas State University Veterinary Medical Teaching Hospital patient population and from surrounding primary care veterinary hospitals. The study was approved by the Institutional Animal Care and Use Committee of Kansas State University and written owner consent was obtained before patient entry into the study.

Inclusion Criteria

Cats were required to have IRIS Stage 2 or early Stage 3 CKD, as indicated by a serum creatinine concentration of 1.6–3.5 mg/dL in a euhydrated state with a concurrent USG <1.030. Short-term stable disease was evidenced by demonstrating <20% change in serum creatinine concentration from initial evaluation to the first follow-up evaluation 10–14 days later to rule out acute kidney disease, acute-on-chronic kidney disease, and prerenal azotemia. The patient's temperament had to be such that the required diagnostic evaluations and drug administration would not cause undue risk to the clinician, veterinary student, technical staff, pet owner, or the cat.

Exclusion Criteria

Cats with evidence of comorbidities or consequences of CKD including bacterial pyelonephritis, neoplasia, nephro- or ureterolithiasis, uncontrolled hyperthyroidism, systemic hypertension requiring treatment (Doppler measured blood pressure >170 mmHg on 2 occasions or >160 mmHg with evidence of target organ damage), or other unrelated disease leading to clinical illness resulted in exclusion. Renal proteinuria was not considered an exclusion criterion.

Study Design

A prospective, randomized, positive-controlled study was conducted. Cats that fulfilled the inclusion criteria were randomly placed into 1 of 3 treatment groups: rhubarb supplement^a (Group I), benazepril^b (Group II), or both (Group III). Rhubarb supplement was initially administered as 75 mg PO q24h and increased to 75 mg PO q12h at 1 month (manufacturer recommended dose^a). The rhubarb supplement dose was based in part on a safety study in which this supplement was administered to over 25 cats with stable CKD (unpublished data).^c Benazepril^b was administered at approximately 0.5 mg/kg PO q24h, with the dose rounded to the nearest 1.25 mg.

Initial Hospital Visit

Initial investigation to diagnose CKD and rule out comorbidities included CBC, serum biochemistry, urinalysis, UPC, species-specific semiquantitative urine albumin ELISA,^d aerobic bacterial urine culture, total thyroxine concentration, thoracic radiography, abdominal radiography and ultrasound examination, and Doppler^e-measured blood pressure. In addition, historical findings, physical examination findings, and body weight were recorded.

Subsequent Hospital Visits

A follow-up examination was scheduled at 10–14 days and if renal excretory function was stable (<20% change in serum creati-

nine concentration), the cat was included in the study. Additional examinations occurred at 1 month after inclusion in the study and every 3 months thereafter. More frequent visits could be scheduled at the discretion of attending clinician, referring veterinarian, or pet owner. A CBC, serum biochemistry, urinalysis, UPC, species-specific semiquantitative urine albumin ELISA,^d and Doppler^e-measured blood pressure were performed at each examination, excluding the CBC which was not performed at the first follow-up visit. In addition, a bacterial urine culture and total thyroxine (TT4) concentration were performed every 6 months and abdominal radiography, ultrasound examination, or both were performed every 12 months. Finally, historical findings, physical examination findings, and body weight were recorded at each visit. Included in the historical findings was information regarding possible adverse effects of the medications and difficulty administering them. Verbal confirmation of medication administration compliance was obtained at each hospital visit.

Blood Sample Collection and Analysis

Pet owners were instructed to withhold food but not water for at least 12 hours before hospital visits. Blood samples were collected from the jugular or medial saphenous vein. Serum biochemistry, CBC, and TT4 were performed on the day of the visit.

Urine Sample Collection and Analysis

All urine samples were collected by cystocentesis. Urinalysis was performed using a refractometer for USG, commercially available reagent strips^f for chemical evaluation, and standard microscopic sediment examination. Approximately 0.5 mL of urine was saved from each urine sample and refrigerated until submitted, on the same day, for aerobic culture and sensitivity. Aerobic urine cultures were performed every 6 months or sooner, if pyuria, bacteriuria, or both were observed in the urine sediment. Urine protein was quantified using the benzethonium reaction method and urine creatinine was quantified using the buffered Jaffe reaction, both with an automated chemistry analyzer.^g The UPC was calculated from this data for each urine sample. The UPC for a specific visit was not included in statistical analysis in the case of (1) pyuria (>10 WBC/hpf), (2) a positive bacterial urine culture, (3) gross hematuria, (4) spermaturia, or (5) bacteriuria, except for the presence of cocci without pyuria or a positive urine culture. In addition, each urine sample was analyzed for microalbuminuria using a commercially available species-specific urine albumin ELISA according to package insert instructions.^d Finally, all urinalyses urine cultures were performed on the day of visit.

Blood Pressure Measurement

Systolic blood pressure measurements were obtained by use of an ultrasonic Doppler^e monitor after the cat was acclimated to the hospital environment. The cat was placed in lateral recumbency. The up forelimb was used for pressure measurement with a neonatal #2 or #3 cuff (width approximately 35–40% the circumference of the leg) placed directly below the elbow. After clipping directly over the common digital branch of the radial artery, 3–4 readings were obtained and the mean was recorded.

Imaging

Thoracic radiographs, abdominal radiographs, and abdominal ultrasound examination findings were interpreted by a board-certified veterinary radiologist. When required, ketamine

(5 mg/kg, IV) and diazepam (0.5 mg/kg, IV) were administered for sedation.

Diet

All cats were exclusively fed a commercially available renal specific diet. All cats were slowly, over at least a 14-day period, transitioned to a renal-specific diet^h if not already consuming the diet starting at the first hospital visit. For cats that did not accept the initially offered commercially available diet, 1 of 2 alternative commercially available diets^{i,j} was offered.

Treatment

Medical treatment of CKD was at the discretion of the attending clinician based on the following guidelines. Although hypertension requiring treatment was an exclusion criterion, if a cat became hypertensive (systolic blood pressure ≥ 170 mmHg on >1 visit or systolic blood pressure >160 mmHg and evidence of target organ damage) after inclusion into the study, amlodipine was started at 0.625 mg PO q24h. The dosage was increased as needed to maintain a systolic blood pressure <160 mmHg. Severe hypokalemia (clinical signs of myopathy) was treated with IV potassium supplementation in the form of potassium chloride followed by PO supplementation. Mild or moderate hypokalemia (serum potassium concentration below reference interval but without signs of myopathy) was treated with PO supplementation on an outpatient basis. Potassium gluconate was prescribed at 2 mEq PO q12h. This dose was increased as needed to maintain serum potassium concentration within the reference interval. If a cat was previously receiving SC fluids at inclusion in the study, this treatment was continued. Bacterial urinary tract infections were treated with an appropriate antibiotic based on urine culture and sensitivity testing and followed up with a repeated bacterial culture within 1 week of discontinuing antibiotic treatment.

Cause of Death

Kidney-related death was defined as death or euthanasia because of the progressive decline of kidney function or the consequences thereof. This classification required documentation of an increased serum creatinine concentration ($>20\%$ from last hospital visit) and clinical signs associated with azotemia including but not limited to anorexia, weight loss, gastrointestinal upset, uremic ulcers, and lethargy. Nonkidney-related death was defined as death or euthanasia, in which there was not a substantial increase in serum creatinine concentration ($<20\%$ from last hospital visit) and an unrelated disease process was determined to play a substantial role in the patient's deterioration.

Statistical Analysis

Analyses were performed using commercial software.^{k,l} Descriptive statistics were presented as mean \pm SD. Age, body weight, hematocrit, blood pressure, serum creatinine concentration, and UPC were compared between groups at enrollment by ANOVA. Mean duration of study enrollment was compared between groups by ANOVA. Change in body weight, hematocrit, blood pressure, serum creatinine concentration, and UPC was compared within groups and between groups over time by repeated measures ANOVA. A treatment by visit interaction term was included in all repeated measures models. All participants were included in the statistical analysis except cats with <3 months of treatment as participants in the study. Significance was set at $P \leq .05$.

The number of cats included in the study was based on an *a priori* power estimate. It was estimated (based on expected population variance, expected mean dependent variable results, estimated clinically relevant differences between dependent variables, and a within-patient correlation of 0.75) that 6 cats in each group would detect a difference in serum creatinine concentration of 0.4 mg/dL, UPC of 0.14, and systolic blood pressure of 10 mmHg at a power of 0.80.

Results

A total of 46 cats were evaluated as possible participants in the study. Six cats were excluded because of an inappropriate degree of azotemia. Five cats were excluded because of systemic hypertension that required medical treatment. Three cats were excluded because of nephro- or ureterolithiasis. Two cats were excluded because of illness from disease not related to CKD including respiratory and gastrointestinal disease, respectively. One cat was excluded because of fractious nature. The remaining 29 cats were enrolled in the study. Three cats that were enrolled in the study were not included in statistical analysis because of <3 months of participation in the study. One of these cats was euthanized for illness associated with pancreatic carcinoma found on postmortem examination. The remaining 2 cats were enrolled for a short period of time because of poor pet owner compliance. A specific reason for poor pet owner compliance in these 2 cats was not reported. Of the cats included in statistical analysis, 9 cats were allocated to the rhubarb only group (Group I), 9 cats to the benazepril only group (Group II), and 8 cats to the rhubarb and benazepril group (Group III). One cat originally allocated to Group II had a presumed severe cutaneous drug reaction to benazepril soon after inclusion into the study. This cat was placed in Group I after a 30-day washout period. Only the data collected for this cat after being allocated to Group I were included in the statistical analysis.

There were no significant differences among treatment groups at entry into the study with respect to body weight, blood pressure, hematocrit, serum creatinine concentration, or UPC (Table 1). The mean \pm SD duration of time that cats were enrolled in the study was 22.1 ± 12.3 months. The mean \pm SD duration of enrollment for Groups I, II, and III was 22.4 ± 15.9 , 25.8 ± 10.1 , and 17.7 ± 9.56 months, respectively. There was no significant difference in duration of time cats were enrolled in the study among treatment groups ($P = .42$). There were no significant differences within or between groups over time with respect to the change in serum creatinine concentration, body weight, hematocrit, blood pressure, or UPC (Table 2, Figs 1–5). While enrolled in the study, 5 cats were euthanized for kidney-related reasons; the numbers of cats from Groups I, II, and III were 1, 2, and 2 cats, respectively. An additional 3 cats were euthanized because of reasons unrelated to the natural progression of CKD; the number of cats from Groups I, II, and III were 1, none, and 2 cats, respectively. The

Table 1. Indirect indicators of renal function at study inclusion in cats with IRIS Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

Clinical Variable	Treatment		P-value
	Group	Mean ± SD	
Serum creatinine concentration (mg/dL)	Overall	2.40 ± 0.44	.365
	Group I	2.41 ± 0.45	
	Group II	2.26 ± 0.45	
	Group III	2.56 ± 0.40	
Indirect systolic blood pressure (mmHg)	Overall	131 ± 16.8	.118
	Group I	139 ± 16.6	
	Group II	122 ± 13.6	
	Group III	130 ± 17.1	
Urine protein: urine creatinine ratio	Overall	0.53 ± 1.09	.656
	Group I	0.23 ± 0.23	
	Group II	0.72 ± 1.28	
	Group III	0.61 ± 1.41	
Hematocrit (%)	Overall	34.8 ± 5.59	.390
	Group I	33.6 ± 5.70	
	Group II	36.7 ± 5.12	
	Group III	34.0 ± 6.12	
Body weight (kg)	Overall	4.76 ± 1.57	.096
	Group I	5.41 ± 1.31	
	Group II	4.91 ± 1.88	
	Group III	3.73 ± 0.99	
Age (months)	Overall	151 ± 52.2	.970
	Group I	125 ± 63.2	
	Group II	152 ± 40.8	
	Group III	179 ± 37.5	

Table 2. Serum creatinine concentration, indirect systolic blood pressure, UPC, hematocrit, and change in body weight over time in cats with Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

Variable	Repeated Measures ANOVA (P-Value)		
	Treatment	Time	Treatment × Time
Serum creatinine	.35	.34	.43
Indirect blood pressure	.90	.22	.37
Urine protein: urine creatinine	.92	.55	.40
Hematocrit	.65	.24	.38
Change in body weight	.71	.23	.37

causes of death in these 3 cats included persistent periuria, bilateral renal transitional cell carcinoma (TCC), and unknown. The cat with periuria had multiple negative aerobic bacterial cultures and crepitus on palpation of multiple joints. This cat failed to improve by providing an additional litter box without a climb-up step and medical treatment for osteoarthritis. The second cat was euthanized because of an acute deterioration in renal function. Bilateral renal TCC was found at necropsy and therefore this euthanasia was not

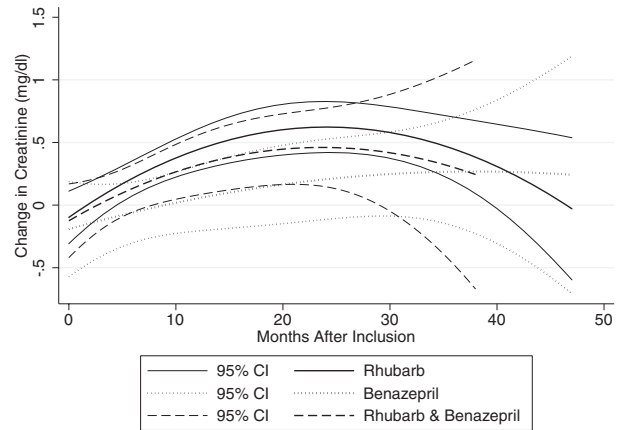


Fig 1. The average change in serum creatinine concentration over time in cats with Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

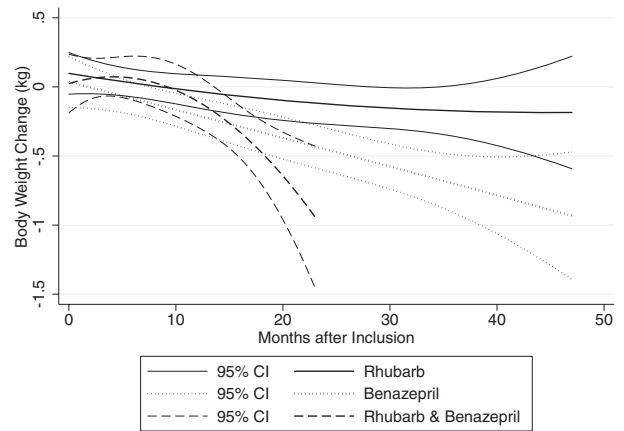


Fig 2. The average change in body weight over time in cats with Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

attributed to natural progression of CKD. A third cat died of unknown causes and no postmortem examination was performed. Based on contemporaneous laboratory results and clinical signs, this death was categorized as nonkidney related. The numbers of all cause deaths in Groups I, II, and III were 3, 2, and 4 cats, respectively. Because of the low rate of kidney-related death, survival analysis was not performed.

One cat, from Group II, required hospitalization and treatment related to CKD. This cat required IV fluids and potassium supplementation. This cat later was euthanized because of complications of CKD. Five cats required PO potassium supplementation^{m,p}; the number of cats from Groups I, II, and III were 3, 1, and 1, respectively. Five cats received SC fluids at home; the number of cats receiving SC fluids for Groups I, II, and III were 2, 2, and 1, respectively. Two cats, both from Group I, developed systemic hypertension after entry into the study which was controlled with PO amlodipine.⁹ The highest recorded

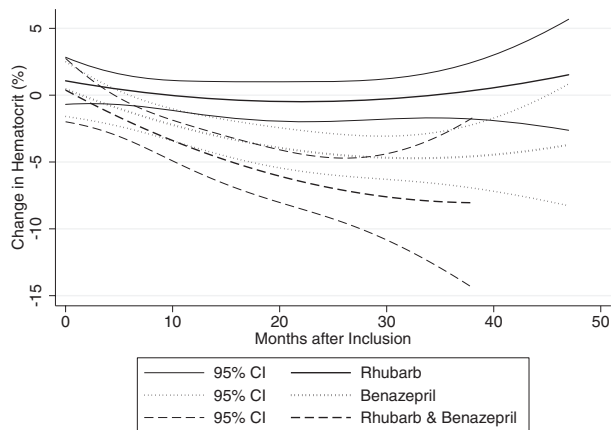


Fig 3. The average change in hematocrit over time in cats with Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

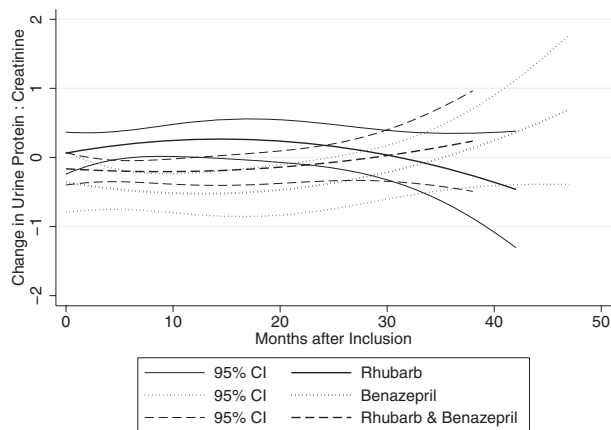


Fig 5. The average change in urine protein: creatinine ratio over time in cats with Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

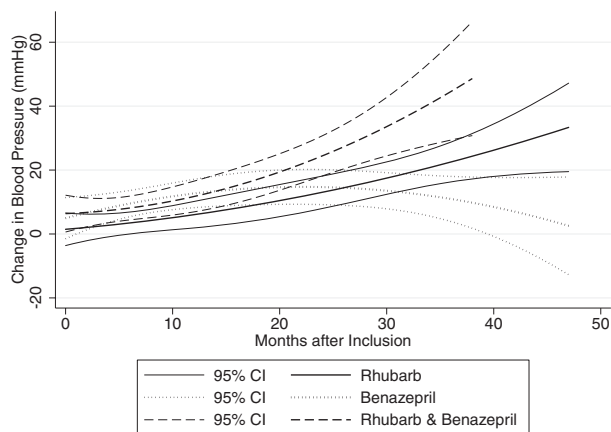


Fig 4. The average change in indirect systolic blood pressure over time in cats with Stage 2 or early Stage 3 CKD treated with Chinese rhubarb (Group I; n = 9), benazepril (Group II; n = 9), or both (Group III; n = 8).

systolic blood pressures were 170 and 175 mmHg, respectively. The time to development of systemic hypertension after entry into the study was approximately 1 and 3 years, respectively. Neither cat had signs of hypertensive encephalopathy on physical examination or hypertensive retinal changes on fundic examination. Two cats, 1 each from Groups II and III, received PO famotidine for gastrointestinal upset.^P Two cats, one each from Groups II and III, received PO methimazole for previously diagnosed hyperthyroidism.^Q Six cats received PO antibiotics for bacterial lower urinary tract infection; the number a of cats from Groups I, II, and III were 1, 2, and 3, respectively. One cat, from Group III, received PO antibiotics for bacterial rhinitis.

Possible adverse effects of rhubarb supplement administration as reported by the pet owner included 2 cats: 1 with lethargy and 1 with vomiting. Both possible adverse effects resolved without specific treatment and rhubarb supplementation was continued. A severe

cutaneous drug reaction was the single possible reported adverse effect associated with benazepril administration. This reaction was manifested as widespread erythema, pruritus, and alopecia, which was most severe on the ventrum. Skin scrapings and cytology evaluation were unremarkable. No additional diagnostic investigation such as skin biopsy was performed. The cutaneous reaction completely resolved in the 2 weeks after discontinuation of benazepril. One pet owner reported difficulty administering the rhubarb supplement tablet. All but 2 cats ate the initial renal-specific diet.^h Both accepted an alternate commercially available renal-specific diet.^{i,j}

Discussion

This study is the first to investigate the effects of a Chinese rhubarb supplement^a on the progression of naturally occurring CKD in cats. The results failed to detect a significant difference among treatment with rhubarb supplement, benazepril, or both with regard to the progression of CKD as quantified by changes in serum creatinine concentration, body weight, hematocrit, systolic blood pressure, and UPC. The IRIS staging system classifies cats with serum creatinine concentration of 2.5–5.0 mg/dL as Stage 3.¹⁹ Cats with IRIS Stage 2 or early Stage 3 CKD (serum creatinine concentration of 1.6–3.5 mg/dL) were chosen for this study. Although this inclusion criterion was arbitrary, cats with later IRIS Stage 3 CKD and beyond, with a potentially greater degree of renal fibrosis already present, were considered less likely to benefit from antifibrotic treatment.

Not finding a significant difference among treatments is only notable with an appropriately powered study. Prestudy power estimates showed that including 6 cats in each group would provide a power of 0.80 for the detection of a 0.4 mg/dL difference in serum creatinine concentrations, a 0.14 difference in UPC, or a 10 mmHg difference in systolic blood pressure. This estimate assumed an intracat correlation over time of

0.75. This study consisted of at least 8 cats per treatment group. As such, there is expected to be at least an 80% chance that if a significant difference existed it would have been detected.

The diagnosis of feline CKD is essentially one of exclusion. Azotemia because of ureteral obstruction, renal neoplasia, pyelonephritis, and prerenal or postrenal causes must be ruled out. A diagnosis of CKD usually includes small irregular kidneys on abdominal palpation and small, irregular kidneys with a loss of corticomedullary definition of abdominal ultrasound examination and usually does not include renal biopsy. As such, it is possible for an underlying renal disease to go undetected. One cat in this study was found to have bilateral renal TCC on postmortem examination. This neoplasm may have been the cause of renal dysfunction in this cat from the beginning. It is also possible that this cat developed renal TCC subsequent or in addition to CKD. The fact that this cat lived for almost 11 months with relatively stable kidney function, that kidney imaging at inclusion was consistent with CKD and not renal neoplasia, and postmortem examination showed both glomerulosclerosis and interstitial nephritis in addition to renal TCC, makes CKD and subsequent renal TCC most likely. For this reason, this cat was included in the final statistical analysis. To the authors' knowledge, renal TCC or other renal neoplasia has never been associated with rhubarb administration in other species including humans or rodents. Although considered unlikely, rhubarb supplement as a cause of renal cancer in this cat cannot be completely ruled out.

As expected, cats with IRIS Stage 2 and early Stage 3 CKD live a relatively long time.²⁰ For this reason, dependent variables other than survival were used to assess response to treatment. Euthanasia is the most common cause of death in cats with CKD and is because of perceived poor quality of life.²⁰⁻²³ All deaths in this study were because of euthanasia. Of the 3 cats that were euthanized for nonkidney-related causes, 1 was euthanized because of persistent periuria. It could be argued that this was at least in part related to CKD secondary to polyuria. Other comorbidities whether related to CKD or not that might predispose a cat to periuria include idiopathic cystitis, urinary tract infection, urolithiasis, urinary tract neoplasia, osteoarthritis, and cognitive dysfunction. This cat had multiple negative bacterial urine cultures and unremarkable urinary bladder ultrasound examination making bacterial cystitis, neoplasia, or urolithiasis unlikely. Osteoarthritis was believed to be present in this cat based on crepitus during joint manipulation. The cat failed to improve with provision of an additional litter box that did not have a climb-up step and medical treatment for osteoarthritis. It was possible that osteoarthritis or reluctance to step up into the litter box initiated the periuria which then became behavioral. Because factors beyond CKD likely played a substantial role in the periuria and subsequent euthanasia in this cat, it was classified as a nonkidney-related death.

A limitation of this study is the duration of time cats were enrolled in the study. The mean duration of enrollment for all cats in this study was approximately 22 months. For case recruitment, referring veterinarians and pet owners received a monetary incentive. The monetary incentive given to the pet owner after 1 year of study participation likely improved compliance and increased the duration of participation. Because of the monetary incentives provided, compliance as it relates to the treatment groups was not further investigated.

A second limitation of this study is that neither pet owners nor investigators were blinded to the treatments and some treatment bias may have occurred. The objective indirect measures of kidney function or consequences thereof, such as serum creatinine concentration, hematocrit, change in body weight, systolic blood pressure, and UPC likely were not affected. Alternatively, the pet owner's perceived quality of life and the decision to euthanize may have been affected.

A third limitation of this study is that GFR was not measured. Serum creatinine concentration indirectly correlates with GFR when certain factors such as lean body mass are held stable.¹⁸ Overall, the cats in this study lost body weight over time. There was no significant difference in body weight among groups at inclusion into the study or in the change in body weight over time. The latter suggests that across groups the effect of the change in body weight as it pertains to serum creatinine concentrations would be similar.

A final limitation of this study is that the benazepril dose was not adjusted based on patient response. Four cats receiving benazepril, 2 each from Groups II and III had UPC persistently ≥ 0.4 . If allowed by study protocol, the benazepril dose may have been increased in these cats. It is possible that allowing for dose escalation of benazepril in this study would have led to improved clinical efficacy in these cats. ACEi may slow the progression of feline CKD, but the evidence is limited.^{24,25} There is more evidence for this effect in other species.²⁶⁻³⁰ Not finding a significant difference among treatment groups suggests that in this population of cats both benazepril and rhubarb affected the progression of CKD similarly or possibly not at all. Without a negative control, it is not possible to make any statement with regard to how the treatments compared to no treatment at all.

The UPC provides prognostic information in feline CKD.^{23,31,32} As such, it would have been reasonable to either stratify or include a certain degree of proteinuria as an exclusion criterion. The inclusion of proteinuric cats was deemed important as studies using rodent models of kidney disease have shown a decrease in proteinuria with the administration of rhubarb extract.^{15,16} In addition, there is evidence that the effects of ACEi and rhubarb on proteinuria and renal fibrosis are synergistic.^{15,16} Although consistent renal proteinuria (UPC >0.4) was uncommon in this study, the authors felt it was unethical to withhold appropriate treatment of proteinuria. For these reasons, benazepril was chosen as the positive control and a third group of cats treated with both drugs was included in

the study. Treatment of systemic hypertension with amlodipine decreases proteinuria,³¹ which may have affected the UPC in the 2 cats from Group I that received amlodipine.

Although the UPC at baseline was not significantly different among treatment groups, this does not necessarily mean that they were not clinically different. In a prospective, longitudinal study of geriatric nonazotemic cats, cats that became azotemic started with a UPC of 0.17 as compared to cats that did not become azotemic with UPC of 0.14.³³ Considering the relatively small difference between groups in the aforementioned study, the difference between Group I (mean UPC 0.23) and Groups II and III (mean UPC 0.72 and 0.61, respectively) in this study may be clinically relevant. It is not possible to discern how the differences in proteinuria among treatment groups affected these study results.

Hematocrit was chosen as an indirect indicator of renal endocrine function. Endocrine dysfunction in the case of a relative lack of erythropoietin can provide important therapeutic and prognostic information.^{23,32} The failure to detect and appropriately treat renal anemia leads to lethargy and other signs of systemic illness readily recognized by the pet owner. Anemia associated with CKD is multifactorial; contributing factors include anemia of chronic disease, shortened red blood cell life span, relative erythropoietin deficiency, and gastrointestinal blood loss.³⁴ In this study, early signs of anemia especially when accompanied by gastric upset were treated with famotidine. Although this treatment was directed toward gastric erosion or ulceration that may develop secondary to hypergastrinemia, no further investigation such as gastrointestinal endoscopy was used to corroborate or refute this assumption. In addition, bone marrow sampling to further investigate nonregenerative anemia was not performed in any cat. Finally, hydration status is patient dependent and may have affected the hematocrit. An alternative to assessing renal endocrine function would have been directly quantifying erythropoietin, which would have been interpreted in light of the cat's hematocrit. At the time of the study, a commercial feline erythropoietin assay was not available.

Systemic hypertension frequently is associated with feline CKD.³⁵ As such, systolic blood pressure was monitored throughout the study. There is no evidence that systemic hypertension is more prevalent as CKD progresses. There is evidence in people with CKD that systemic hypertension contributes to deterioration of renal function.³⁶ Although the role of systemic hypertension in the progression of CKD in cats is not well established, there is some histopathologic evidence that it may negatively affect prognosis.³⁷ Control of systemic hypertension in cats with CKD may improve survival in part by decreasing proteinuria.³¹ We felt it was unethical to withhold amlodipine treatment to cats with hypertensive CKD. To decrease confounding bias and variability and increase power in this study, we tried to select a homogenous population of cats with CKD. Cats had variable

clinical monitoring before the study, and it is possible that cats with systemic hypertension at the first visit may have had long-term systemic hypertension. For these reasons, cats with systemic hypertension were excluded from the study. During the study, only 2 cats developed systemic hypertension, and they did so approximately 1 and 3 years after entry, respectively. Both cats were considered at moderate risk for target organ damage based on the degree of systemic hypertension and neither had evidence of complications.¹⁹ Because of the frequent monitoring of cats in this study, the amount of time the cats could have been hypertensive was short. For these reasons, the 2 cats that developed systemic hypertension were not removed from the study.

One cat in Group II was reallocated to Group I. The fact that this group change contradicted the goals of random allocation and intention-to-treat was recognized, although the effect to the overall randomness of the study was considered very small. A total of 17 cats in this study received rhubarb for a mean duration of approximately 20 months. As stated previously, it is considered unlikely that rhubarb supplementation was the cause of renal TCC in 1 cat in this study, although it cannot be completely ruled out. Only 2 additional cats showed mild findings that were possible adverse effects of rhubarb administration, suggesting that the rhubarb supplement used in this study is likely safe to administer over a relatively long period of time to cats with Stage 2 or early Stage 3 CKD.

Conclusion

Based on the analysis of easily measured clinical indirect indicators of renal excretory and endocrine function, this study failed to find a significant difference in the progression of feline CKD among cats treated with benazepril, rhubarb supplementation, or both at commonly recommended dosages. Further investigation of the effects of rhubarb supplementation as it relates to specific subsets of cats with CKD is warranted.

Footnotes

- ^a Rubenal, Vetoquinol USA, Fort Worth, TX
- ^b Benazepril, Teva Pharmaceuticals USA, North Wales, PA
- ^c Rubenal Technical Brochure, Vetoquinol USA
- ^d E.R.D. Health Screen Urine Tests, Heska, Loveland, CO
- ^e Ultrasonic Doppler Flow Detector, Parks Medical Electronics Inc, Aloha, OR
- ^f Bili Labstix, Bayer Healthcare LLC., Morristown, NJ
- ^g Hitachi 911, Roche Diagnostics, Indianapolis, IN
- ^h k/d, Hill's Pet Nutrition, Topeka, KS
- ⁱ NF Kidney Function, Purina Veterinary Nutrition, St. Louis, MO
- ^j Renal LP, Royal Canin USA, St. Charles, MO
- ^k STATA 11, STATA Corp LP, College Station, TX
- ^l SAS on Demand, SAS, Cary, NC

^m Renal K, Vetoquinol USA

ⁿ Tumul K, JMI-Daniels Pharmaceuticals, St. Petersburg, FL

^o Amlodipine besylate, Ascend Laboratories LLC, Montvale, NJ

^p Famotidine, Teva Pharmaceuticals USA, Sellersville, PA

^q Methimazole, Par Pharmaceutical Companies Inc, Spring Valley, NY

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