

# Effects of an Intestinal Phosphorus Binder on Serum Phosphorus and Parathyroid Hormone Concentration in Cats With Reduced Renal Function

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**KEY WORDS:** feline, kidney, phosphorus, nutrition

## ABSTRACT

Ten young adult cats, 6 intact males and 4 intact females, with reduced renal mass were randomized to receive either normal feline maintenance diet alone or diet plus phosphorus binder in a crossover design with each treatment period of 56 days in duration (Dietary Trial A). For Dietary Trial B, following a 3-month withdrawal period, 6 cats were placed on the intestinal phosphorus binder for 9 months to determine the long-term effects of this approach. During both Dietary Trials A and B, cats were studied by serum and urine biochemical testing and renal clearance studies. In Dietary Trial A, compared to diet alone, serum phosphorus and plasma parathyroid hormone concentrations were significantly lower when intestinal phosphorus binder was provided. There were no significant differences in blood urea nitrogen, serum creatinine concentration, glomerular filtration rate, or renal plasma flow. In Dietary Trial B, serum phosphorus and plasma parathyroid hormone concentrations were reduced at the 6- and 9-month

time points of the treatment period compared to measurements obtained before intestinal phosphorus binder administration. We conclude that the addition of an intestinal phosphorus binder to a normal maintenance feline diet can lower serum phosphorus and parathyroid hormone concentrations in cats with International Renal Interest Society stages I and II chronic kidney disease. The effect of the binder to reduce serum phosphorus concentration was present by Day 56 in Dietary Trial A and persisted at 6 and 9 months in Dietary Trial B.

## INTRODUCTION

Phosphorus retention and renal secondary hyperparathyroidism are common complications of feline chronic kidney disease (CKD).<sup>1-3</sup> Hyperphosphatemia has been associated with the development of renal structural lesions and renal secondary hyperparathyroidism in laboratory studies in rats,<sup>4</sup> dogs,<sup>5</sup> and cats<sup>6</sup> with induced kidney disease. In cats with spontaneous CKD, hyperphosphatemia is a negative prognostic factor.<sup>7,8</sup> Laboratory<sup>6</sup> and clinical<sup>1,2</sup> studies in cats have identified a renoprotective effect of dietary phosphorus restriction.

In a previous study, aged cats with spontaneous CKD were fed a maintenance feline ration combined with an intestinal phosphorus binder.<sup>9</sup> Results indicated that the binding agent was associated with reduced intestinal availability of phosphorus and reductions in plasma urea and phosphate concentrations. However, control animals were normal cats and it was difficult to separate time and treatment effects in this study. We hypothesized that hyperphosphatemia and renal secondary hyperparathyroidism could be managed in cats with early CKD through the addition of an intestinal phosphorus binding agent to a maintenance feline ration.

## **METHODS**

### **Animals**

Ten 8- to 11-month-old cats (4 intact females, 6 intact males) initially weighing  $3.64 \pm 0.20$  kg were procured from a commercial supplier (Liberty Research Inc., Waverly, New York, USA). Each cat's health was assessed by physical examination and determinations of plasma concentrations of blood urea nitrogen (BUN), serum creatinine (SCr), and the urine protein-to-creatinine ratio.

### **Animal Preparation**

All cats underwent right nephrectomy and infarction of approximately 5/6 of the left kidney by ligation of a variable number of branches of the renal artery, a procedure hereafter referred to as 11/12 nephrectomy,<sup>6,10</sup> approximately 6 months prior to the dietary trials.

### **Diets**

The cats were fed a canned feline maintenance diet (Purina Pro Plan Chicken and Liver Adult Cat Entrée, Nestle Purina PetCare Co., St Louis, Missouri, USA) throughout both Dietary Trials of the study and this diet contained approximately 0.47% phosphorus, 0.50% calcium, and 76% moisture on an as-fed basis. The cats were offered a pre-weighed amount of food daily, initially 35 kcal/kg body weight twice daily, with food being provided between 0800-1000h and between 1500-1700h daily. Daily

food intake was determined and amount of food provided was adjusted on a monthly basis with a goal of maintaining a stable body weight.

### **Phosphorus Binder**

A commercially available intestinal phosphorus binder containing chitosan and calcium carbonate (Epakitin, Vetoquinol, Buena, New Jersey, USA) was utilized in this study. The binder was mixed with food and provided twice daily at a dosage of 1 g for each meal for cats weighing <5 kg and 2 g twice daily for cats weighing >5 kg.

### **Dietary Trial A**

Approximately 6 months after renal mass reduction, the 10 cats were randomly divided into 2 groups of 5 each. For Days 1-56, cats in Group 1 received diet alone and cats in Group 2 received diet plus phosphorus binder. For Days 57-112, the groups were crossed over so that Group 1 received diet plus phosphorus binder and Group 2 received diet alone. Biochemical measurements were obtained prior to 11/12 nephrectomy (pre), at the time of division into treatment groups before drug administration (Day 0), and at Days 26, 56, 84, and 112. Glomerular filtration rate (GFR), renal plasma flow, and fractional excretion of phosphorus measurements were obtained at Days 0, 56, and 112. Serum parathyroid hormone concentration (PTH) was determined prior to 11/12 nephrectomy (pre) and on Days 56 and 112.

### **Dietary Trial B**

Six cats (2 males and 4 females) with International Renal Interest Society (IRIS) stages I or II CKD were selected from the original group of 10 for inclusion in a second dietary trial of 15 months' duration. For this trial, the cats received diet (Purina Pro Plan Chicken and Liver Adult Cat Entrée, Nestle Purina PetCare Co., St Louis, Missouri, USA) only for 3 months (time -3 to 0 months), diet plus binder for 9 months, and subsequently diet only for 3 months. Immediately prior to institution of binder administration (Month 0) and at 3, 6, 9, and

12 months later, SCr, serum phosphorus, serum calcium, BUN, PTH, GFR, and urine protein-to-creatinine ratio measurements were obtained.

### Biochemical Measurements

Blood was obtained by venipuncture for subsequent measurement of serum concentrations of phosphorus, calcium, BUN, and SCr. Serum analyte determinations were obtained by a semi-automated device (Spectrum CCX, Abbott Diagnostics, Irving, Texas, USA).

### Renal Clearance Studies

The GFR and renal plasma flow were estimated as urinary clearance of exogenously administered creatinine and para-aminohippuric acid, respectively, utilizing a previously described procedure.<sup>10</sup> During this procedure, urine was obtained by urethral catheterization for urinalysis and determination of the urine protein-to-creatinine ratio. Serum and urine creatinine and urine protein determinations were obtained by a semi-automated device (Spectrum CCX, Abbott Diagnostics, Irving, Texas, USA). Serum and urine concentrations of para-aminohippuric acid was determined by a chemical method.<sup>10</sup> Fractional clearance of phosphorus (%) was determined during these procedures as  $100 \times \text{urinary phosphorus excretion (mg/min)}/\text{GFR (mL/min)} \times \text{serum phosphorus concentration (mg/mL)} / \text{filtrate phosphorus content}$ .

### Statistical Analysis

Values are reported as mean  $\pm$  SEM. Statistical analyses were performed with the aid of a commercial software package (Statview 4.5, Abacus Concepts, Inc., Berkeley, California, USA). Statistical comparisons were by analysis of variance with inclusion of an effect for drug treatment and time (if multiple measurements were made) in the model. If a statistically significant global effect was observed, pairs of group means were compared by Fisher's protected least significant different test. A *P* value of  $<0.05$  was taken as indicative of a statistically significant difference.

## RESULTS

### Dietary Trial A

The mean body weight for the 10 cats was  $3.85 \pm 0.28$  kg on Day 0, prior to treatment. The average quantity of food offered was  $120.5 \pm 8.3$  g per cat and there were no significant treatment or time effects in quantity of food offered, food intake, or body weight (Table 1). The initial mean values for parameters (Day 0) for cats in this trial were  $3.36 \pm 0.27$  g albumin/dL,  $35.1 \pm 3.6$  IU alanine transferase/L,  $154 \pm 2$  mEq sodium/L,  $3.6 \pm 0.1$  mEq potassium/L,  $18.0 \pm 0.8$  mmol bicarbonate/L,  $28.0 \pm 3.3$  IU alkaline phosphatase/L, and  $2.1 \pm 0.1$  mg magnesium/dL. The hematocrit averaged  $27.2\% \pm 1.2\%$  and the urine specific gravity was  $1.023 \pm 0.003$ . There was no significant time or treatment effect for these serum and urine parameters during Dietary Trial A.

On Day 0, GFR was  $1.42 \pm 0.11$  mL/min/kg body weight and renal plasma flow was  $5.00 \pm 0.34$  mL/min/kg. Analysis of serum of the 10 cats revealed mean values of  $5.85 \pm 0.22$  mg phosphorus/dL,  $10.4 \pm 0.1$  mg calcium/dL,  $2.56 \pm 0.12$  mg creatinine/dL, and  $45.5 \pm 2.7$  mg BUN/dL on Day 0. There were no significant treatment or time effects on SCr, BUN, GFR, or renal plasma flow. There was a significant ( $P < 0.05$ ) treatment effect on serum phosphorus concentration and urinary fractional clearance of phosphorus during the trial with lower values for both observed during administration of the intestinal phosphorus binding agent (Table 1). Compared to diet alone, provision of the intestinal phosphorus binder was associated with a significantly ( $P < 0.05$ ) lower PTH of approximately 46% overall. However, the mean PTH in cats with reduced renal mass fed the binder remained significantly ( $P < 0.05$ ) greater than results of measurements obtained in the cats prior to renal mass reduction ( $2.9 \pm 0.5$  pmol/L).

### Dietary Trial B

Following a 3-month washout period, the cats were provided with a mean phosphorus binder intake of  $0.21 \pm 0.02$  g/kg body

weight twice daily for 9 months (Months 0-9). The cats then received diet alone for 3 months. There was no significant treatment or time effect on food intake or body weight. Compared to Month 0, the mean values for serum phosphorus were lower ( $P < 0.05$ ) at 6 and 9 months (Table 2). While 4 of 6 cats had serum phosphorus concentrations between 4.5 mg/dL and 5.1 mg/dL after 3 months of administration of the intestinal phosphorus binding agent, all serum phosphorus concentrations were between 3.0 and 4.5 mg/dL for Months 6 and 9. There were no significant treatment or time effects on other serum biochemical parameters, GFR, or the urine protein to-creatinine ratio.

In a previous laboratory study utilizing the remnant kidney model of CKD in cats, ingestion of a phosphorus supplemented diet exacerbated hyperphosphatemia and hyperparathyroidism and was associated with more severe renal structural lesions.<sup>6</sup>

A more recent study of spontaneous feline CKD demonstrated that elevated serum phosphorus concentration was associated with a shorter survival time in cats with CKD.<sup>8</sup> Dietary phosphorus restriction coupled with the use of an aluminum-based intestinal phosphorus binding agent reduced serum phosphorus, reduced plasma PTH concentration, and increased median survival time.<sup>2</sup> As a consequence of these and

**Table 1:** Results at the end of a 56-day treatment period of measurements of parameters in cats with reduced renal mass fed diet alone or diet plus intestinal phosphorus binder in Dietary Trial A.

Parameter	Diet Alone	Diet Plus Binder
Number of cats	10	10
Food intake (g/kg body weight)	106 ± 7	107 ± 7
Phosphorus binder intake (g/kg body weight, twice daily with food)	0	0.23 ± 0.02
Body weight (kg)	3.83 ± 0.26	3.84 ± 0.24
GFR (mL/min/kg body weight)	1.49 ± 0.11	1.41 ± 0.09
Renal plasma flow (mL/min/kg body weight)	4.88 ± 0.78	4.69 ± 0.56
SCr (mg/dL)	2.54 ± 0.05	2.68 ± 0.07
BUN (mg/dL)	42.7 ± 1.2	43.5 ± 1.7
Serum phosphorus (mg/dL)	5.55 ± 0.11	5.14 ± 0.11*
Serum calcium (mg/dL)	10.4 ± 0.1	10.4 ± 0.1
Serum parathyroid hormone (pmol/L)	15.3 ± 1.6	8.3 ± 1.2*
Urinary fractional clearance of phosphorus (%)	38.6 ± 4.1	27.9 ± 2.9*
Urine protein/creatinine ratio	0.42 ± 0.05	0.42 ± 0.08

GFR = glomerular filtration rate; SCr = serum creatinine; BUN = blood urea nitrogen.

\* $P < 0.05$  vs corresponding mean value for diet alone.

## DISCUSSION

Our study demonstrated an effect of an intestinal phosphorus binder to lower serum phosphorus concentration, PTH, and urinary fractional excretion of phosphorus in cats fed a maintenance feline diet. This effect was observed in both a 56-day crossover trial and during a 9-month trial in a subset of these cats. The cats were fed a maintenance diet with phosphorus content higher than typically recommended<sup>11</sup> for azotemic cats.

other studies of phosphorus homeostasis in CKD, dietary phosphorus restriction is routinely recommended for cats with azotemic CKD corresponding to IRIS stages II-IV.<sup>11</sup>

A previous study<sup>9</sup> of the same intestinal phosphorus binding agent in cats, which included 6 older animals with spontaneous azotemia, demonstrated a reduction in apparent digestibility of phosphorus. In that study, both BUN and plasma phosphorus concentration decreased when the cats were provided the intestinal phosphorus binder.

**Table 2:** Results of measurements of parameters in cats with reduced renal mass fed diet plus intestinal phosphorus binder for Months 0-9 and diet alone for Months 10-12 in Dietary Trial B. The cats received diet alone for 3 months prior to the initiation of this trial.

Parameter	0 Months	3 Months	6 Months	9 Months	12 Months
Number of cats	6	6	6	6	6
Body weight (kg)	3.88 ± 0.34	3.85 ± 0.30	3.88 ± 0.26	3.90 ± 0.30	3.85 ± 0.29
GFR (mL/min/kg)	1.40 ± 0.15	1.36 ± 0.08	1.35 ± 0.07	1.37 ± 0.11	1.34 ± 0.13
SCr (mg/dL)	2.50 ± 0.16	2.68 ± 0.16	2.77 ± 0.14	2.50 ± 0.16	2.62 ± 0.15
BUN (mg/dL)	38.2 ± 3.2	43.2 ± 4.2	35.0 ± 3.3	35.8 ± 3.1	41.8 ± 2.4
Serum calcium (mg/dL)	10.9 ± 0.1	10.9 ± 0.2	10.7 ± 0.1	10.9 ± 0.1	10.5 ± 0.1
Serum phosphorus (mg/dL)	5.0 ± 0.22	4.62 ± 0.31	3.52 ± 0.26*	3.87 ± 0.23*	4.73 ± 0.19
Serum parathyroid hormone concentration (pmol/L)	12.7 ± 2.9	7.9 ± 1.4	5.3 ± 0.9*	4.9 ± 1.2*	9.0 ± 1.2
Urine protein/creatinine ratio	0.33 ± 0.06	0.39 ± 0.06	0.41 ± 0.03	0.35 ± 0.05	0.34 ± 0.04

GFR = glomerular filtration rate; SCr = serum creatinine; BUN = blood urea nitrogen.

\* $P < 0.05$  vs corresponding value for 0 months.

As a feline maintenance diet was also used in this previous study, the authors suggested that this approach could be an alternative treatment option for cats refusing to ingest diets specially formulated for CKD. While our study demonstrated a decrease in serum phosphorus concentration with a similar dietary approach, there was no apparent effect of the binding agent on BUN, SCr, GFR, renal plasma flow, or proteinuria. We did not establish the long-term effects of the use of a maintenance diet plus intestinal phosphorus binder on the preservation of renal structure and function in cats. Thus, we are not advocating the use of the present dietary approach as an alternative to specially formulated diets. It is important to note that studies<sup>1,12</sup> of cats with spontaneous IRIS stages II and III CKD demonstrated a beneficial effect of dietary modification, specifically a decrease in uremic episodes, renal-related deaths, or prolonged survival. The beneficial effects observed in these studies may have been due to modified phosphorus content to other dietary variables present. Nonetheless, cats with CKD may find specially formulated diets to be less acceptable or owners may offer a mixture of diets and if so, our study confirmed previous results<sup>9</sup> that a reasonable degree of control of phosphorus metabolism can be achieved with the addi-

tion of an intestinal phosphorus binder to a feline maintenance diet, particularly in IRIS stages I and II.

Our study demonstrated that cats with azotemia equivalent to IRIS stages I and II CKD and very mild changes in serum phosphorus concentration had serum phosphorus concentrations lowered after the addition of an intestinal phosphorus binding agent while being fed a normal feline maintenance diet. It may be beneficial to lower serum phosphorus concentration below the upper level of the normal range in dogs and cats with CKD. The goal for control of serum phosphorus concentration in CKD has been proposed to be as low as 4.5 mg/dL.<sup>11</sup> At 6 and 9 months of administration during Dietary Trial B, we achieved this level of control in the cats with induced azotemia comparable to IRIS stages I and II. Cats with more severe azotemia, comparable to IRIS stages III and IV, are unlikely to achieve this level of control of serum phosphorus concentration with the present dietary approach.

Hyperparathyroidism is present in CKD and has been linked to uremia or disease progression in various studies in other species.<sup>13-15</sup> In the present study, the addition of the intestinal phosphorus binding agent to a canned maintenance feline diet reduced the magnitude of hyperparathyroidism.

However, compared to values obtained in the same cats on the same diet prior to renal mass reduction, the PTH remained elevated. Control of serum phosphorus concentration and prolongation of survival in cats with CKD has previously been associated with reduction of PTH.<sup>2</sup>

The addition of an intestinal phosphorus binding agent to food may reduce food intake in azotemic cats. In the present study, this particular agent containing calcium carbonate and chitosan had no such effect. In summary, the addition of an intestinal phosphorus binding agent to a canned feline maintenance diet reduced serum phosphorus and PTH in cats with induced azotemia equivalent to IRIS stages I and II.

#### ACKNOWLEDGEMENTS

This study was funded, in part, by Vetoquinol, Buena, New Jersey, USA.

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