Long-Term Safety of Urine Acidifying Diets for Cats

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Introduction

Clinical signs associated with feline lower urinary tract disease (FLUTD) have been recognized for many years. FLUTD can be roughly categorized as those diseases associated with urolithiasis (approximately 24%), with urethral plugs (approximately 22%), or idiopathic (approximately 55%).[1] In the late 1800s, evidence was collected which suggested that urolithiasis affected approximately 0.22% of the cat population.[2] In 1985, Lawler and others reported that the incidence of all types of FLUTD was not greater than 0.85% of the population.[3] Scientists documented that several different types of uroliths have been found in cats; however, the predominant uroliths have been struvite (magnesium ammonium phosphate hexahydrate) and more recently, calcium oxalate.[4]

In an attempt to manage FLUTD through dietary manipulation, scientists have focussed on struvite urolithiasis and mineral content of the diet. Experiments indicated that diets containing high levels of magnesium (0.5 - 1.0%) induced urolithiasis and urinary tract obstruction.[5,6] This led to recommendations that dietary magnesium (Mg) be limited to < 20 mg Mg/kcal of metabolizable energy (ME); however, experimental diets used in these studies contained Mg in excess of levels in commercial cat foods and the chemical source of dietary magnesium (MgO) influenced urine pH and confounded experimental results.[5,6] Buffington and others reported that consumption of a diet containing MgO resulted in struvite formation and obstruction, whereas ingestion of a diet containing $MgCl_2$ resulted in a lack of struvite crystals.[7]

Urine pH below 6.6 has been shown to be a much more important factor in maintaining the solubility of struvite crystals.[7,8] More recent experiments have demonstrated that the use of selected ingredients and addition of urine acidifying agents can effectively allow the production a urine pH below 6.6 in most cats.[9]

Prevalence of struvite uroliths submitted to the Minnesota Urolith Center has been decreasing during the past decade.[10] This is thought to be primarily from the incorporation of urine acidifying ingredients into commercial cat foods that help provide a low urine pH.[11] Sources of animal protein and corn gluten meal contain sulphur amino acids (methionine and cysteine), which may be metabolized to sulphate and excreted in the urine as acidic metabolites.[9]

Increased use of urine acidifying formulations, however, has led to increased concern regarding potential adverse effects of dietary acidification on systemic metabolic homeostasis. Potential adverse effects include taurine depletion, potassium depletion, metabolic acidosis, and increased incidence of calcium oxalate urolithiasis.[10,12-15] Dow and others reported that adding 0.8% ammonium chloride to a potassium-restricted (0.2%) diet induced metabolic acidosis and potassium depletion.[13] Osborne and coworkers reported an increased prevalence of calcium oxalate uroliths submitted to the Minnesota Urolith Center.[10] Diets formulated to reduce the risk of struvite formation may induce metabolic acidosis thus causing an increase in calcium excretion and may increase the incidence of other uroliths, especially calcium oxalate.[10]

The objective of this experiment was to determine the long-term safety of diets that use urine acidifying ingredients to promote low urine pH.

Materials and Methods

CATS, DIETS, AND FEEDING PROCEDURES

Thirty-six adult female Domestic Shorthair cats, age 2 to 6 years, were allotted to three treatments groups. Groups were striated such that initial bodyweight and

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TABLE 1
Ingredient List of Diets in Order of Predominance

Diet 1	Diet 2	Diet 3
corn	corn gluten meal	corn gluten meal
corn gluten meal	corn	corn
soybean meal	chicken	animal fat
chicken	animal fat	poultry byproduct meal
animal fat	wheat flour	wheat flour
wheat flour	rice	rice
rice	dried whole eggs	soybean meal
calcium carbonate	phosphoric acid	phosphoric acid
phosphoric acid	calcium carbonate	calcium carbonate
salt	salt	salt
dried whey	sodium caseinate	dried whey
dried animal digest	dried whey	dried animal digest
defluorinated phosphate	dried animal digest	defluorinated phosphate
potassium chloride	defluorinated phosphate	potassium chloride
vitamin premix	potassium chloride	vitamin premix
mineral premix	vitamin premix	mineral premix
taurine	mineral premix	taurine
lysine	taurine	lysine
	lysine	

age were not different between groups. Cats were housed individually in stainless steel cages in a controlled environment and monitored over a 2 year period.

Groups were assigned to one of three diets (Table 1). Diet 1 was formulated to be a non-acidifying diet. Diets 2 and 3 were formulated to promote an acidic urine and were designed to be representative of several commercially available products. All diets were formulated to provide similar nutrition (Table 2). Gradations in titratable acidity indicated that the correct trend in dietary acidity was present. Cats were fed ad libitum throughout the test period except when fasted or fed a meal for certain sample collections as noted below. Fresh water was available at all times.

DATA COLLECTION

Physical examinations were conducted to confirm the health status of each cat prior to initiation of the study and at subsequent 6-month intervals throughout the study. Cats were weighed initially and at 28-day intervals, and individual food consumption was recorded daily. Blood and urine samples were taken initially and periodically throughout the 2-year period

TABLE 2
Chemical Composition of the Experimental Diets (Dry Matter Basis)

Assay	Diet 1	Diet 2	Diet 3
crude protein, %	36.01	35.50	35.32
crude fat, %	18.26	16.70	15.28
calcium, %	1.07	1.01	1.23
phosphorus, %	0.97	0.93	1.04
potassium, ppm	8,544	8,115	8,388
sodium, ppm	3,532	2,547	2,480
chloride, %	0.61	0.92	0.95
magnesium, ppm	1,316	801	838
sulfate, ppm	4,730	3,349	3,279
titratable acidity	0.99	1.14	1.37
taurine (calculated), ppm	1,667	1,695	1,843

(Table 3). Urine samples were collected from cats by cystocentesis with sedation (Ketamine HCL, 10 mg/lb bodyweight, IM) after ad libitum feeding and after meal feeding. Ad libitum urine samples were collected as follows: Food and litter pans were removed from cages at 8 a.m. Urine was collected at approximately 11 a.m. Meal-fed urine samples were collected as follows: Cats were fasted (16 hours) overnight. At 8 a.m. litter pans were removed and cats were fed their respective diets. Urine was collected via cystocentesis, 3 hours post-prandially at approximately 11 a.m. from cats that had consumed at least 15 g of their ration. Venous blood samples were also collected by jugular vena puncture. A pH meter was used to determine urine and blood pH within 30 minutes of collection. Complete urinalyses were performed including pH, specific gravity and sediment analysis. Sediment was evaluated for the presence of crystals and was assigned a score based on subjective concentration of crystals (none, occasional, light, moderate, heavy).

Blood samples were taken periodically from fasted (16 hours) or meal-fed cats as indicated in Table 2. Bone mineral density was measured at termination of the experiment by dual energy X-ray absorptiometry (DEXA:Lunar Corp, Madison, WI). Fifty-three normal adult cats from the Purina Pet Care Center cat colony were also analyzed for bone mineral density to establish reference values.

STATISTICAL ANALYSIS

Urine pH values and all blood variables from ad libitum and meal-fed cats were analyzed separately for each collection period using a one-way analysis of var-

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TABLE 3
Blood and Urine Sampling Schedule

		Weeks																
		0	4	8	16	24	26	32	39	48	52	54	65	66	79	91	92	104	106
Blood samples:																			
Hematology	fasted	x		x	x	x		x		x		x		x	x		x		x
Serum biochemical profile	fasted	x										x		x	x		x		x
Venous blood gases	fasted	x										x		x	x		x		x
Plasma taurine	fasted											x		x	x		x		x
Serum ionized calcium	fasted											x		x	x		x		x
Parathyroid hormone	fasted											x		x	x		x		x
Hematology	meal-fed		x				x		x		x		x			x		x	
Serum biochemical profile	meal-fed		x				x		x		x		x			x		x	
Venous blood gases	meal-fed		x				x		x		x		x			x		x	
Urine samples:																			
pH, sediment, specific gravity	ad libitum		x				x		x		x		x			x		x	
	meal-fed		x				x		x		x		x			x		x	

TABLE 4
Effect of Diet on Bodyweight and Food Intake

	Diet 1	Diet 2	Diet 3
Bodyweight, kg[1]			
Initial	3.22 ± 0.35	3.20 ± 0.29	3.53 ± 0.29
Final	3.92 ± 0.38	4.25 ± 0.46	3.65 ± 0.35
Change	0.7 ± 0.20[ab]	1.05 ± 0.36[a]	0.11 ± 0.17[b]
Daily food intake, g	53.2 ± 0.85	54.2 ± 1.42	53.8 ± 1.22
M.E. kcal/day	204.3	211.4	206.6

[1]Least squares means ± standard error
[ab]Means within rows with different superscripts differ ($p < 0.05$)

lance. An analysis of the combined weeks (4, 26, 39, 52, 65, 91, and 104) was completed using analysis of variance for repeated measures. The change in blood values among treatments from 0 to 106 weeks was tested using one-way analysis of variance. Multiple comparisons among treatment means were made using least significant differences. Analysis of the frequency of urine crystals was completed using a score test for ordinal categorical response on repeated measures. Differences were considered significant at $p < 0.05$ and data in tables and figures are expressed as least squares means ± standard error.

Results

One cat from Diet 1 was removed from test because of chronic colitis. Three cats assigned to Diet 2 were removed from the test. One cat assigned to Diet 2 was removed within 2 months because of a pre-existing health problem. One cat died an accidental death not related to treatment. The third cat was removed from Diet 2 because of consistent refusal to eat. One cat assigned to Diet 3 developed severe pancreatitis and was removed from test. Physical examinations indicate that all three treatment groups remained generally healthy with the exceptions noted above.

Cats maintained or increased in bodyweight throughout the 2-year experiment. Bodyweight increase was greatest in cats consuming Diet 2 (Table 4).

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TABLE 5
Effect of Diet on Selected Blood Values of Fasted Cats[1]

	Unit	Diet 1	Diet 2	Diet 3	Reference Ranges
Calcium	mg/dL	8.25 ± 0.10	8.07 ± 0.13	8.15 ± 0.10	7.9 - 10.0
Potassium	mmol/L	4.32 ± 0.05	4.22 ± 0.07	4.17 ± 0.05	3.66 - 5.04
Magnesium	mEq/L	1.93 ± 0.03	1.85 ± 0.04	1.90 ± 0.03	1.6 - 3.0
Phosphorus	mg/dL	4.02 ± 0.10[a]	3.95 ± 0.13[a]	3.64 ± 0.11[b]	3.3 - 6.5
Plasma taurine	μmol/L	92.6 ± 6.68	115.1 ± 8.67	107.4 ± 6.78	75 - 267
Ionized calcium	mmol/L	1.24 ± 0.02	1.26 ± 0.02	1.24 ± 0.02	1.0 - 1.4
Parathyroid hormone	pmol/L	1.17 ± 0.12	1.50 ± 0.14	1.26 ± 0.12	0 - 4.0

[1]Least squares means ± standard error
[ab]Means within rows with different superscripts differ ($p < 0.05$)

TABLE 6
Effects of Diet on Blood Gas Values of Fasted and Meal-Fed Cats[1]

		Units	Diet 1	Diet 2	Diet 3	Reference Ranges
Base Excess						
	meal-fed	mmol/L	−2.87 ± 0.44[a]	−4.52 ± 0.44[b]	−4.92 ± 0.41[b]	−8.0 - 0.2
	fasted	mmol/L	−4.86 ± 0.48	−5.48 ± 0.65	−5.01 ± 0.49	
Bicarbonate						
	meal-fed	mmol/L	22.47 ± 0.40	21.21 ± 0.41	20.67 ± 0.38	18.2 - 26.2
	fasted	mmol/L	20.50 ± 0.40	20.18 ± 0.55	20.19 ± 0.49	
pH						
	meal-fed	unit	7.31 ± 0.011	7.28 ± 0.011	7.30 ± 0.01	7.23 - 7.37
	fasted	unit	7.30 ± 0.007	7.29 ± 0.01	7.31 ± 0.008	
Total CO_2						
	meal-fed	mEq/L	24.05 ± 0.47	22.87 ± 0.48	22.11 ± 0.44	19.5 - 27.6
	fasted	mEq/L	22.00 ± 0.53	21.59 ± 0.72	21.67 ± 0.54	

[1]Least squares means ± standard error
[ab]Means within rows with different superscripts differ ($p < 0.05$)

Hematology and serum biochemical profiles remained within established colony reference intervals. The only significant difference between treatment means was in serum phosphorus (Table 5).

Combined analysis of venous blood gas data collected from meal-fed cats over the 2-year period showed that all values remained within colony reference ranges; however, base excess and bicarbonate were significantly lower for Diet 2 and Diet 3 than Diet 1 (Table 6).

Mean urine pH from cats fed ad libitum was lower ($p < 0.05$) for Diets 2 and 3 than for Diet 1 at Weeks 26, 39, 65, 91, and 104 (Fig. 1), while meal-fed urine pH values were lower for Diets 2 and 3 only at the 26-week sampling period (Fig. 2). Combined analysis of urine pH revealed that ad libitum-fed cats receiving Diet 2 or Diet 3 had lower ($p < 0.05$) urine pH than those fed Diet 1 (Table 7). Combined data for meal-fed cats showed a similar directional trend with urine pH being significantly lower on Diet 3 than Diet 1 (Table 7). Urine specific gravity was not affected by dietary treatment (Table 7). Urine sediment values indicated there were lower incidences of moderate to heavy struvite crystal formation with Diets 2 and 3 than Diet 1 when cats were fed their respective diets ad libitum (Table 8).

There were no dietary treatment effects on bone mineral density (Table 8). All bone mineral density values were within colony reference ranges.

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TABLE 7
Effect of Diet on Mean Urine pH and Urine Specific Gravity[1]

	Diet 1	Diet 2	Diet 3
Ad libitum:			
urine ph	6.58 ± 0.10[a]	6.24 ± 0.09[b]	6.21 ± 0.09[b]
urine specific gravity	1.048 ± 0.0008	1.048 ± 0.0008	1.047 ± 0.0007
Meal-fed:			
urine pH	7.21 ± 0.14[a]	7.05 ± 0.12[a]	6.87 ± 0.12[b]
urine specific gravity	1.047 ± 0.0012	1.047 ± 0.0011	1.047 ± 0.0011

[1]Least squares means ± standard error
[ab]Means within rows with different superscripts differ ($p < 0.05$)

TABLE 8
Effect of Diet on Bone Mineral Density[1]

	N	g/cm^2	S.E.
Diet 1	10	0.560	± 0.012
Diet 2	9	0.541	± 0.014
Diet 3	11	0.560	± 0.011
Colony average	53	0.559	± 0.042

[1]Least squares means ± standard error

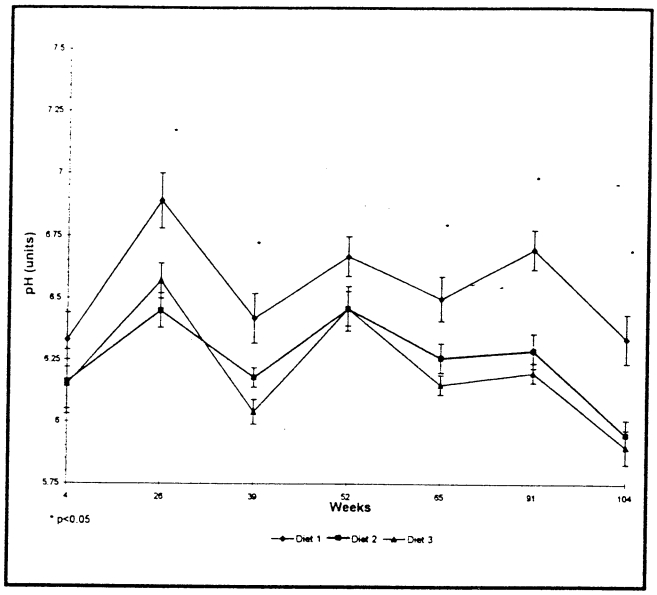

FIG. 1 — Effect of diet on urine pH of ad libitum fed cats.

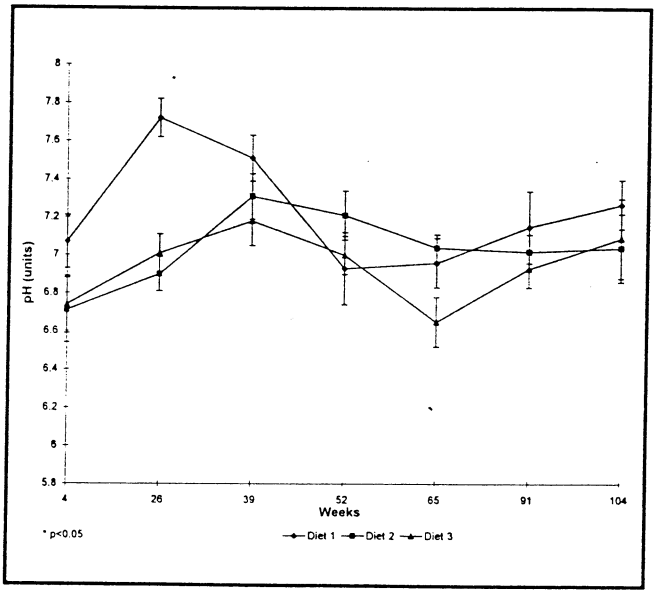

FIG. 2 — Effect of diet on post-prandial urine pH.

Discussion

Previous studies demonstrated that diets containing ammonium chloride can induce metabolic acidosis, lower urine pH, and reduce Ca, K and Mg excretion.[13,15] Dietary ammonium chloride supplementation in cats has been shown to decrease absorption of potassium and induce a negative dietary potassium balance.[13] Skoch and others had reported that diet supplementation with phosphoric acid effectively reduces urine pH when cats are fed ad libitum.[9] Other ingredients such as corn gluten meal and poultry meal were reported to be potent acidifying food components.[9] The experimental diets used in this study utilized a combination of potentially urine acidifying ingredients to maintain a low urine pH throughout the 2-year study. This lends support to previously published reports that animal proteins and corn gluten meal, which contain sulphur-containing amino acids that are metabolized and excreted as acidic metabolites, contribute to the acidification potential of the diet.

Our results indicate that ad libitum feeding is essential to maintain a mean urine pH less than 6.5. During the post-prandial alkaline tide, meal-fed cats typically produced a urine pH approximately 0.5 to 1.0 pH units greater than ad libitum-fed cats. When food is available continuously, cats may consume 10 to 20 small meals throughout a 24-hour period.[16] This feeding pattern minimizes the amount of gastric acid secretion for each small meal and decreases the post-prandial alkalinization of the urine. In addition, cats fed ad libitum have increased frequency of urination and greater total urine volume than meal-fed cats.[17] This may be beneficial in minimizing urolith formation.

Bone mineral density was measured at the end of the 2-year study. No significant differences in bone

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mineral density were found among dietary treatments nor with the reference colony average. These results support previous observations that bone turnover and calcium metabolism are not significantly affected by moderate dietary acidification.[18]

Conclusion

Diets formulated to include urine acidifying ingredients achieved a moderate degree of urine acidification (pH 6.0 - 6.5) when fed ad libitum and maintained the health of cats over the 2-year experiment. There were no adverse effects noted on systemic acid-base homeostasis, plasma taurine, or bone mineral density. During the course of the 2-year study, it appeared that the cats adapted metabolically to the urine acidifying diets and maintained acid-base homeostasis. ■

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Abstract

Effects of Choreito Consumption on Struvite Crystal Growth in Urine of Cats

The effect of a dietary supplement, choreito, on in vitro struvite cyrstal growth in feline urine was evaluated. Adult specific-pathogen-free cats (four females, four males) considered to be clinically normal on the basis of physical examination findings and normal results of CBC, serum biochemical analyses, and urinalyses obtained before the beginning of the study were used. Before 24-hour urine sample collections were made, cats were fed a commercial canned diet with 0 or 500 mg of choreito supplement/kg of bodyweight for at least 2 weeks in a cross-over design with four cats/treatment. Filtered urine samples were analyzed for urine pH, specific gravity, osmolality, and urine electrolytes. The struvite activity product was calculated, using a statistical software program that calculates urine saturation. Urine samples were placed in wells of cell culture plates, increasing concentrations of ammonium hydroxide were added to adjacent wells to stimulate struvite crystal growth, and the plates were incubated at 37°C. Crystal growth was assessed by determination of number of crystals and supersaturation index by direct visualization, using an inverted microsope. Supplementation of the diet with choreito (at this concentration) did not change urine pH, specific gravity, osmolality, urine electrolyte composition, or calculated struvite activity product. However, supplementation significantly ($P < 0.05$) reduced crystal number and supersaturation index. These results indicate that direct observation of struvite crystal formation in whole urine may more accurately predict the effects of treatments to prevent or treat struvite urolithiasis than do calculations based on electrolyte concentration that do not account for the effect of urine macromolecules. It also may mean that choreito consumption affects the concentration of inhibitors or promoters in urine. It was concluded that choreito significantly ($P < 0.05$) reduced growth of struvite crystals in feline urine, and thus may have a role in prevention of feline struvite urolithiasis. In vivo studies will be necessary to test this hypothesis.

Abstracted from: Buffington CA, Blaisdell JL, Komatsu Y, Kawase K: Effects of Choreito Consumption on Struvite Crystal Growth in Urine of Cats. Am J Vet Res 55(7):972-975, 1994.