Influence of Prednisolone on Urinary Calcium Oxalate and Struvite Relative Supersaturation in Healthy Young Adult Female Domestic Shorthaired Cats

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CLINICAL RELEVANCE

Prednisolone (10 mg PO q24h) or placebo was administered to healthy cats for 2 weeks in a masked, placebo-controlled, crossover-design study, and 24-hour urine samples were collected. When cats received prednisolone, 24-hour urine pH was lower and 24-hour urine excretion of creatinine, magnesium, phosphate, and potassium was higher than when cats received placebo. No significant difference was found in urinary relative supersaturation for calcium oxalate (CaOx) or struvite between treatment groups. Prednisolone administration did not induce diuresis, nor was it associated with increased calcium excretion or urinary saturation for CaOx in these healthy cats. Results of this study, however, should not be extrapolated to cats that form CaOx uroliths associated with idiopathic hypercalcemia.

INTRODUCTION

Urolithiasis is common in cats, and calcium oxalate (CaOx) is the second most common mineral in uroliths, occurring in approximately 39% of urinary bladder stones and more than 90% of nephroliths.1 Of cats affected with CaOx urolithiasis, 15% to 35% have concurrent hypercalcemia, usually idiopathic in nature.1 Although CaOx-preventive diets are available, they are not uniformly successful, particularly in cats with idiopathic hypercal-
The purpose of this study was to determine the influence of prednisolone on urinary excretion of calcium and oxalic acid and urinary saturation with CaOx in healthy cats. We hypothesized that prednisolone administration would increase urinary calcium excretion and urinary saturation with CaOx in healthy cats.

**MATERIALS AND METHODS**

**Cats**

Five healthy, 10- to 12-month-old intact female domestic shorthaired research cats weighing 2.27 to 4.01 kg were evaluated. Clinically normal cats were selected based on physical examination, complete blood cell counts (Advia 120, Siemens, Tarrytown, NY), plasma biochemical analysis (concentrations of albumin, bicarbonate, urea nitrogen, calcium, chloride, cholesterol, creatinine, glucose, phosphate, potassium, sodium, total bilirubin, and total protein; activities of alanine aminotransferase

<table>
<thead>
<tr>
<th>TABLE 1. Guaranteed Analysis and Ingredient List of the Diet* Consumed by Cats (n = 5) in This Study</th>
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</thead>
<tbody>
<tr>
<td><strong>Crude protein</strong></td>
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<tr>
<td><strong>Crude fat</strong></td>
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<tr>
<td><strong>Crude fiber</strong></td>
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<tr>
<td><strong>Moisture</strong></td>
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<tr>
<td><strong>Energy</strong></td>
</tr>
<tr>
<td><strong>Ingredients</strong></td>
</tr>
</tbody>
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*SportMix Original Recipe for Cats, Midwestern Pet Foods, Evansville, IN; formulation as of 2005.
and aspartate aminotransferase; and calculated anion gap; Hitachi 911, Roche Laboratories, Indianapolis, IN), urinalysis, and aerobic bacteriologic urine culture. The proposal was approved by The University of Tennessee Institutional Animal Care and Use Committee (IACUC protocol #1461).

**Study Design**

To minimize differences attributable to individual cats over time, a masked, placebo-controlled crossover design was used to evaluate the effect of prednisolone on urinary RSS for CaOx monohydrate (RSScom), CaOx dihydrate (RSScod), and struvite (magnesium ammonium phosphate hexahydrate; RSSmap).11 Cats were fed a single lot of a commercially available diet (SportMix Original Recipe for Cats, Midwestern Pet Foods, Evansville, IN; formulation as of 2005; see Table 1 for nutritional analysis). The amount of diet initially fed was based on calculated daily caloric requirements12 determined by body weight (BW; $100 \times BW_{kg}^{0.75}$) and adjusted to maintain BW throughout the study. Cats were randomized using a random numbers table13 to receive either prednisolone or placebo for 2 weeks:

- **Prednisolone**: 10 mg/ml liquid suspension at 2.2 mg/kg PO q24h
- **Placebo**: The same volume of a lactose-containing solution formulated to appear similar to the prednisolone suspension via the addition of food coloring

After the 2-week treatment period, urine samples were collected and administration of prednisolone and the placebo were discontinued for a washout period of 1 week. Cats were then crossed over to the other treatment group for 2 weeks, after which urine samples were again collected.

**Housing**

Cats were housed in a room together except during the 24-hour urine-collection periods. During the urine-collection periods, cats were housed in individual cages, and a modified litter pan was used that permits the separation of feces from urine to facilitate the collection of timed urine samples.14,15

**Sample Collection and Analysis**

Blood samples were collected at the beginning of the study by jugular venipuncture; complete blood cell counts (Advia 120), blood ionized calcium (IRMA, ITC, Edison, NJ), and plasma biochemical analysis (Hitachi 911) were conducted at The University of Tennessee College of Veterinary Medicine Clinical Pathology Laboratory using automated analyzers. Urine was collected by antepubic cystocentesis for complete urinalysis and aerobic bacteriologic urine culture.

**Urinary Measurements**

Estimation of urinary RSS requires a timed urine sample. To begin the collection, the urinary bladder of each cat was palpated; if urine was present, cystocentesis was performed to remove it. All urine voided by the cat over the next 24 hours was collected in sealed flasks containing thymol to inhibit bacterial contamination and growth. Every 6 hours, containers were emptied into a larger collection container, which was refrigerated during the collection period. Cystocentesis was performed again at the end of the

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*Of cats affected with CaOx urolithiasis, 15% to 35% have concurrent hypercalcemia.*
24-hour collection period if the bladder palpably contained urine. Urine calcium, chloride, creatinine, magnesium, phosphate, potassium, and sodium were analyzed using an automated analyzer (Hitachi 911; conducted at The University of Tennessee College of Veterinary Medicine Clinical Pathology Laboratory). Urine pH was determined using a combination pH electrode (Orion 90Aplus pH/ISE meter and pH electrode, Orion Research, Beverly, MA). Urine citric acid and oxalic acid were determined using ion chromatography.16,17 Urinary ammonia was determined using an ion-select electrode (Orion 920Aplus pH/ISE meter and Orion model 95-12 Ammonia electrode, Orion Research).18

**Estimation of Urinary Relative Supersaturations**

Twenty-four–hour urinary excretion of various analytes was calculated, and urinary saturation was determined using a computer program designed to estimate RSS (EQUIL 89d, University of Florida College of Medicine). Molar concentrations were entered into the computer program for determination of RSScom, RSScod, and RSSmap.

**Statistical Analyses**

Mean, standard deviation, and P values were calculated on microcomputer statistical software (Statview, SAS Institute, Cary, NC).

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**TABLE 2. Comparison of Urinary Analyte Excretion, Urine Volume, Urine pH Value, and Estimate of Urinary Saturation for Calcium Oxalate Monohydrate (RSScom), Calcium Oxalate Dihydrate (RSScod), and Struvite (RSSmap) in 24-Hour Urine Samples Obtained from Healthy Cats (n = 5) Receiving Prednisolone (10 mg PO q24h) or Placebo***

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Prednisolone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume (ml/kg/24h)</td>
<td>25.7 ± 5.1</td>
<td>30.4 ± 5.2</td>
<td>.09</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.81 ± 0.40</td>
<td>6.08 ± 0.09</td>
<td>.019a</td>
</tr>
<tr>
<td>Ammonia (mM/kg/24h)</td>
<td>0.36 ± 0.18</td>
<td>0.22 ± 0.15</td>
<td>.15</td>
</tr>
<tr>
<td>Calcium (mg/kg/24h)</td>
<td>0.19 ± 0.05</td>
<td>0.33 ± 0.18</td>
<td>.13</td>
</tr>
<tr>
<td>Chloride (mEq/kg/24h)</td>
<td>5.55 ± 0.69</td>
<td>5.98 ± 0.98</td>
<td>.28</td>
</tr>
<tr>
<td>Citric acid (mg/kg/24h)</td>
<td>2.77 ± 1.07</td>
<td>3.11 ± 1.19</td>
<td>.21</td>
</tr>
<tr>
<td>Creatinine (mg/kg/24h)</td>
<td>44.7 ± 3.3</td>
<td>59.3 ± 7.8</td>
<td>.032a</td>
</tr>
<tr>
<td>Magnesium (mg/kg/24h)</td>
<td>1.43 ± 0.40</td>
<td>3.67 ± 1.48</td>
<td>.011a</td>
</tr>
<tr>
<td>Oxalic acid (mg/kg/24h)</td>
<td>2.09 ± 0.42</td>
<td>2.29 ± 0.69</td>
<td>.22</td>
</tr>
<tr>
<td>Phosphate (mg/kg/24h)</td>
<td>61.40 ± 6.46</td>
<td>78.00 ± 6.31</td>
<td>.005a</td>
</tr>
<tr>
<td>Potassium (mEq/kg/24h)</td>
<td>3.89 ± 0.39</td>
<td>4.56 ± 0.65</td>
<td>.045a</td>
</tr>
<tr>
<td>Sodium (mEq/kg/24h)</td>
<td>3.89 ± 0.51</td>
<td>4.47 ± 0.70</td>
<td>.11</td>
</tr>
<tr>
<td>RSScom</td>
<td>0.36 ±0.33</td>
<td>0.62 ± 0.42</td>
<td>.34</td>
</tr>
<tr>
<td>RSScod</td>
<td>0.47 ± 0.38</td>
<td>0.49 ± 0.40</td>
<td>.89</td>
</tr>
<tr>
<td>RSSmap</td>
<td>0.38 ± 0.32</td>
<td>1.59 ± 0.88</td>
<td>.07</td>
</tr>
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</table>

*Data are presented as mean ± 1 SD.

aSignificant difference (P < .05) vs. placebo.
Paired t-tests were used to assess differences in urinary electrolyte and mineral excretion and urinary RSS during the administration of prednisolone or placebo. All paired t-tests with P values < .05 were considered significant.

**RESULTS**

All cats readily ate the diet, and no problems were encountered with treatment administration. Additionally, no adverse events were observed. BW did not change significantly between study periods (P = .9). Significant differences were not found for any analyte between treatment groups. No significant differences were found for 24-hour urine volume or excretion of ammonia, calcium, chloride, citric acid, oxalic acid, or sodium (Table). Significant differences were found for 24-hour urine creatinine, magnesium, pH, phosphate, and potassium (Table 2). No significant differences were found for RSScom, RSScod, or RSSmap (Table 2).

**DISCUSSION**

Urolith formation is a complex process. At a basic level, it involves urinary oversaturation with the compounds that precipitate from solution to form insoluble crystals. Despite urinary oversaturation, uroliths do not always form because of inhibitors of crystal and urolith formation. Over the past two decades, the Minnesota Urolith Center has observed substantial increases in the number of cats with CaOx uroliths. Approximately one-third of cats affected with CaOx uroliths have hypercalcemia. Hypercalcemia would result in increased urinary calcium excretion and possibly urine oversaturation with CaOx; therefore, decreasing blood calcium concentration to normal should be associated with decreased urinary excretion of calcium and a decreased risk of forming CaOx uroliths.

In one study, prednisolone administration was associated with a decrease in serum calcium levels in cats with idiopathic hypercalcemia. In this retrospective study, five of 20 cats received oral prednisone (one cat received 5 mg/day, three cats received 10 mg/day, and one cat received 12.5 mg/day). Serum total calcium and/or ionized calcium normalized in four cats receiving oral prednisolone; however, one cat did not respond. One of the mechanisms thought to be involved in lowering serum calcium concentration is an increase in urinary excretion of calcium; however, in-
cant increase in urine acidity during treatment with prednisolone but no significant increase in urinary saturation with CaOx. An explanation for this might be that the increase in excretion of phosphate, magnesium, and potassium inhibited CaOx formation by forming complexes with calcium despite the aciduria; however, this finding could also be related to the short duration of the study. Long-term administration of prednisolone may result in whole-body depletion of electrolytes and requires further evaluation.

Prednisolone administration was associated with an increase in RSSmap despite inducing aciduria. Urinary pH is thought to be the major influence of struvite crystal and stone formation in cats.30,31 No obvious explanation exists for this paradoxical finding, although urinary phosphate and magnesium excretion were increased with prednisolone administration, which may increase urinary saturation for struvite.

Prednisolone administration resulted in a 33% increase in urinary creatinine excretion. This may represent increased muscle catabolism induced by prednisolone, although BW did not change over the short term. With long-term administration, prednisolone could result in loss of lean muscle mass.

There are several drawbacks to this study. A small number of young adult female cats were evaluated. CaOx urolithiasis occurs more commonly in cats between the ages of 7 and 10 years, with a gender distribution of 59% in males and 41% in females; therefore, our study population is not representative of cats that typically form CaOx uroliths. Furthermore, cats in this study were clinically healthy and did not have a history of urolith formation. Study periods were 2 weeks long with a 1-week washout period. Food restriction results in decreased fecal calcium excretion, which returns to baseline within 7 days of reintroduction of food; however, urinary calcium excretion is minimally affected over the same periods.32 Thus, the lack of finding an influence of 2 weeks’ administration of prednisolone on urinary calcium excretion and urinary saturation for CaOx may be related to the short duration of the study and washout periods. Collecting timed urine samples from cats can be difficult. While frequent urinary catheterization of dogs ensures adequate collection of

The results of this study showed no significant increase in excretion of calcium or urinary saturation with CaOx during administration of prednisolone.

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urine with minimal loss, urinary catheterization in cats requires sedation but has been used for collection of 24-hour urine samples.33 Alternative techniques for collection of timed urine samples in cats include cystocentesis10 and use of modified collection pans for voided samples.10,15,34,35 Because cats typically produce less than 100 ml of urine/day, loss of a few milliliters may result in analytical error. Collecting urine over several days decreases error introduced by incomplete urine collection. The collection technique used in this study has been utilized previously.10

CONCLUSION

Results of this study indicate that prednisolone treatment may not increase the risk for CaOx urolithiasis in healthy young adult female cats as was hypothesized; however, this
was a small study of young adult healthy female cats and cannot be extrapolated to cats that spontaneously form CaOx uroliths and have associated idiopathic hypercalcemia. Further studies with older adult cats and cats with spontaneously occurring CaOx urolithiasis and concurrent idiopathic hypercalcemia are required. Long-term studies to evaluate safety are required as well.

REFERENCES


