Journal of Zoo and Wildlife Medicine 42(3): 426–429, 2011

THE EFFECTS OF A PROBIOTIC ON BLOOD UREA NITROGEN AND CREATININE CONCENTRATIONS IN LARGE FELIDS

Stephanie McCain, D.V.M., Matthew C. Allender, D.V.M., M.S., Juergen Schumacher, Dr. med. Vet., Dipl. A.C.Z.M., Dipl. E.C.Z.M. (Herpetology), and Edward Ramsay, D.V.M., Dipl. A.C.Z.M.

Abstract: Chronic kidney disease is a common finding in older captive exotic felids. The purpose of this study was to evaluate the effectiveness of a probiotic to reduce blood urea nitrogen and creatinine in large felids. Fifteen adult, large felids (6 tigers [*Panthera tigris*], 5 lions [*Panthera leo*], 3 cougars [*Puma concolor*], and 1 leopard [*Panthera pardus*]) were administered a probiotic twice daily after a baseline complete blood cell count and plasma chemistry panel was obtained. Plasma chemistry values were rechecked at 2 mo ($n = 14$) and 6 mo ($n = 9$). There was no significant change in blood urea nitrogen over time; however, there was a significant change in creatinine over time ($P = 0.04$). Creatinine concentration decreased significantly between 2 and 6 mo ($P = 0.02$), and a decrease was seen between 0 and 6 mo, but this change was not significant ($P = 0.05$). There was no significant difference noted for creatinine concentration between 0 and 2 mo ($P = 0.35$). This probiotic may be helpful in large felids with elevated creatinine concentrations because of chronic kidney disease; however, further studies are warranted.

Key words: Azotemia, *Felis, Panthera,* probiotic, renal.

INTRODUCTION

Chronic kidney disease is a common finding in older exotic felids in captivity.[1,9] Clinical signs can include polyuria, polydipsia, decreased appetite, weight loss, and vomiting. Animals often become dehydrated and may develop hypertension.[9] Traditional methods used to manage domestic cats with chronic kidney disease, such as frequent fluid therapy and protein-restricted diets, are often difficult or impractical in large felids.

Recently, an oral probiotic (Azodyl®, Vetoquinol USA, Buena, New Jersey 08310, USA) became available for management of domestic animals with chronic kidney disease. It is composed of live bacterial organisms (Kibow Biotics,® Kibow Biotech, Philadelphia, Pennsylvania 19104, USA, [*Enterococcus thermophilus, Lactobacillus acidophilus, Bifidobacterium longum*]) that metabolize urea nitrogen and creatinine in the gastrointestinal tract, both of which increase secondary to chronic kidney disease. Because these compounds pass from the blood into the gastrointestinal tract based on a concentration gradient, removing them from the gastrointestinal tract would help decrease the concentration of urea nitrogen and creatinine in the blood. The goal is to minimize the clinical consequences of azotemia, not treat the underlying cause of renal disease. Limited data are available on the probiotic's efficacy in domestic cats (*Felis catus*);[2] however, given the prevalence of chronic kidney disease in large felids and the difficulty in treating them, this probiotic has the potential to be useful in the management of chronic kidney disease in these species. Our preliminary experience of using this probiotic in 2 exotic felids with azotemia because of chronic kidney disease resulted in reduced blood urea nitrogen (BUN) and creatinine concentrations at recheck examinations up to 2 yr later.

The aim of this study was to evaluate the effectiveness of the probiotic on decreasing BUN and creatinine concentrations in large felids. Our hypothesis was that daily administration of the probiotic would significantly decrease BUN and creatinine concentrations in large felids.

MATERIALS AND METHODS

This study was approved by The University of Tennessee's Institutional Animal Care and Use Committee. The study population was selected from a collection of approximately 285 large felids, including cougars (*Puma concolor*), leopards (*Panthera pardus*), lions (*Panthera leo*), and tigers (*Panthera tigris*). Initial criteria for evaluation were apparently healthy cats older than 12 yr of age, which resulted in a total of 45 cats being evaluated. After a 24-hr fast, anesthesia was induced with a combination of midazolam (0.05–0.1 mg/kg i.m. or p.o.) (Hospira, Inc., Lake

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, The University of Tennessee, Knoxville, Tennessee 37996, USA. Present address: (McCain) Birmingham Zoo, 2630 Cahaba Road, Birmingham, Alabama 35223, USA; (Allender) Department of Comparative Biosciences, University of Illinois, Urbana, Illinois 61802, USA. Correspondence should be directed to Dr. McCain (smccain@birminghamzoo.com).

Table 1. Descriptive statistics for blood urea nitrogen and creatinine over time in large felids treated with a probiotic. Mean, median, and range for blood urea nitrogen and creatinine are reported in mg/dl.[a]

		Blood urea nitrogen			Creatinine		
Mo	*n*	Median	10–90% percentiles	Min/max	Mean ± SD[b] or median[c]	95% CI[b] or 10–90% percentiles[c]	Min/max
0	15	48	39.8–88.2	38–93	3.6 ± 0.593[b]	2.41–4.79[b]	3.0–4.9
2	14	49.5	36.5–98.5	34–101	3.45[c]	3.0–4.85[c]	3.0–5.2
6	9	42	36–135	36–135	3.04 ± 0.770[b]	1.5–4.58[b]	2.3–4.6

[a] Min, minimum; max, maximum; SD, standard deviation; CI, confidence interval.
[b,c] Mean and confidence intervals were determined for normally distributed data; and medians and 10% and 90% quartiles for non-normally distributed data.

Forest, Illinois 60045, USA), medetomidine or dexmedetomidine (20–30 μg/kg or 15–20 μg/kg, respectively, i.m.) (Domitor® or Dexdomitor®, Pfizer Animal Health, Exton, Pennsylvania 19341, USA), with or without ketamine hydrochloride (1–4 mg/kg i.m.) (Ketaset®, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA), based on an estimated body weight, via hand injection or remote drug delivery system. A blood sample was obtained from the lateral tail, medial or lateral saphenous, or jugular vein, and placed in 2 Vacutainer tubes, (BD Vacutainer® tubes, BD Diagnostics, Franklin Lakes, New Jersey 07417, USA) one with ethylenediamine tetra-acetic acid (EDTA) for complete blood cell count analysis and one with lithium heparin for plasma chemistry analysis. The medetomidine or dexmedetomidine was reversed with atipamezole i.m. (Pfizer Animal Health) at 5 mg for every 1 mg of medetomidine or 0.5 mg dexmedetomidine given. Inclusion criteria for the study were a BUN $\geq$38 mg/dl, a creatinine $\geq$3.0 mg/dl, and no other signs of systemic illness based on blood work and physical examination findings. The parameters for BUN and creatinine were determined by reviewing blood work (analyzed by The University of Tennessee College of Veterinary Medicine's Clinical Pathology Laboratory) from large felids with confirmed chronic kidney disease. Each cat in the study then was administered the probiotic (2 capsules in the morning, 1 in the evening, p.o., based on manufacturer recommendations for domestic cats) until the conclusion of the study. Plasma chemistry panels were repeated at 2 mo (n = 14) and 6 mo (n = 9) by using similar anesthetic protocols at each evaluation.

Summary statistics were computed by using PASW 18.0 (SPSS Inc., Chicago, Illinois 60606, USA). Tests for normality of data were performed on each of the parameters under investigation by using the Shapiro-Wilk test. Mean and confidence intervals were determined for normally distributed data and medians and 10% and 90% quartiles for non-normally distributed data. Nonparametric analysis was used to assess group differences. A Friedman test was performed to determine differences over time. Creatinine concentrations between specific times were compared by using the Wilcoxon signed rank test. A value of $P < 0.05$ was considered significant.

RESULTS

Fifteen cats that ranged in age from 12–18 yr (mean, 15 yr) were included in the study, which included 6 tigers, 5 lions, 3 cougars, and 1 leopard. All the cats ate well throughout the study period and accepted the medication well, and no vomiting or other adverse effects were reported. Because of these cats being housed outdoors, and often with other cats, water consumption and urination patterns were not evaluated. All 15 cats were sampled at time 0, but only 14 cats were sampled at 2 mo, and 9 cats were sampled at 6 mo. One cat was euthanized before the 6-mo time point because of a diagnosis of pulmonary blastomycosis. Unfortunately, a complete necropsy was not performed. The remaining cats were withdrawn from the study by the owner because of concerns over stress related to multiple anesthetic events and not because of physical health concerns or declining condition. All 14 surviving cats were bright, alert, and free of clinical signs at the conclusion of the study period.

Descriptive statistics are summarized in Table 1. Creatinine concentrations decreased significantly (P = 0.04) over time, whereas BUN concentrations were not significantly different at any time point (P = 0.88). When evaluating specific time frames, there was a significant decrease in creatinine concentrations between 2 and 6 mo (P = 0.02). Creatinine concentration decreased between 0 and 2 mo and between 0 mo and 6 mo; however, these decreases were not significant (P = 0.35 and P = 0.05, respectively).

DISCUSSION

The probiotic used in this study is designed to reduce BUN and creatinine concentrations in the blood but will not treat the underlying cause of azotemia. A study that involved 5/6th nephrectomized rats showed a slower progression of azotemia in animals supplemented with probiotic.[4] A similar study in minipigs showed a reduction in BUN but not creatinine.[5] Preliminary evaluation of the probiotic in 7 domestic cats showed reduction in both BUN and creatinine; however, 6 of 7 cats also received fluid therapy and/or nutritional therapy, which made evaluation and comparison with the study reported here difficult.[2]

Preliminary studies of the effects of probiotic supplementation for the management of chronic kidney disease in humans have shown promising results.[3,6,7] These studies have identified a significant reduction in urea nitrogen but not creatinine,[3,7] which is contrary to the findings of the current report. The reasons for this difference are unclear but may relate to a relatively high normal urea nitrogen in large felids compared with domestic felids or humans, although this is purely speculative. Similar to the current report, these studies also had small sample sizes, which were recognized as limitations.[3,7]

The probiotic dose used in this study was based on recommendations designed for domestic cats and dogs, however, given the limited data on its efficacy in domestic animals, we chose not to use an increased dose to compensate for the larger body size of the cats in this report. Our preliminary experience of using this probiotic at this same dose in 2 exotic felids with azotemia because of chronic kidney disease resulted in reduced BUN and creatinine concentrations. Future studies should consider evaluating the effects of a higher dose.

The large felids in the current study did not have any diet changes nor did they receive any treatment for azotemia or chronic kidney disease other than the probiotic. No animals received any other medications (i.e., nonsteroidal anti-inflammatories or antibiotics) during the study period. Results showed a significant decrease in creatinine but not BUN concentrations over time in large felids treated with a probiotic. It is important to note the limitations of this study, including small sample size, multiple species included, a lack of negative controls, and no definitive diagnosis of chronic kidney disease. Renal biopsies, urinalyses, and blood pressure measurements were not performed to definitively diagnose or characterize the severity of chronic kidney disease. This study evaluated only changes in BUN and creatinine concentrations over time.

The findings of this study suggest that 2 mo is too soon to evaluate changes in creatinine. It is possible that the mechanisms by which the probiotic may reduce circulating concentrations of BUN and creatinine require more than 2 mo to take effect. The exact mechanisms of this phenomenon are unknown but may be because of metabolism of the probiotic, site of action, or individual variation. Creatinine concentrations in 8 of the 14 cats sampled at 2 mo increased, although not significantly, compared with the initial concentrations, whereas only 3 decreased and 3 remained unchanged, which may have contributed to the difference that was seen between 2 and 6 mo but not 0 and 6 mo.

Although creatinine concentration decreased significantly over time, other contributing factors may include hydration status, normal plasma creatinine fluctuation, and diet. Without a negative control group, we cannot rule out other factors that contribute to a decrease in creatinine concentration. Given the progressive nature of chronic kidney disease, it seems unlikely that the decrease was a factor of time alone. The impact of several cats being withdrawn from the study is unknown.

The effects of anesthesia on BUN and creatinine concentrations also are unknown. Although we were unable to find reports of the effects of midazolam or ketamine on BUN or creatinine, medetomidine has not been shown to affect BUN or creatinine in dogs.[8] Neither the effects of medetomidine nor dexmedetomidine on BUN or creatinine in felids have been investigated, to our knowledge. Water was withheld from all the animals before anesthesia, which would affect their hydration status. Although this was done similarly before each sample collection, we cannot rule out changes in hydration status that contributed to changes in either value. Ideally, blood samples would be collected voluntarily from awake animals without restricting access to water; however, this was not possible in the cats of the present study.

To identify animals for this study, older cats (>12 yr of age) that were more likely to be azotemic were sampled. The cats in this study were not exhibiting clinical signs at the time of sample collection; therefore, we are unable to draw any conclusions on the effects of the probiotic on clinical signs, which emphasizes the point that frequent monitoring of large felids is

necessary to identify subclinical chronic kidney disease and to develop an appropriate long-term management plan.

In conclusion, creatinine but not BUN significantly decreased over time in large felids treated with a probiotic for azotemia. This probiotic may be helpful in large felids with elevated creatinine because of chronic renal failure; however, further studies are necessary. Future investigations should aim to increase statistical power, evaluate different dosages and time frames, and verify results with monitoring other kidney function tests.

Acknowledgments: Funding for this study was provided by Vetoquinol USA and the Companion Animal Fund, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, The University of Tennessee. We would like to thank the staff at Tiger Haven exotic cat sanctuary for their technical assistance.

LITERATURE CITED

1. Newkirk, K. M., S. J. Newman, L. A. White, B. W. Rohrbach, and E. C. Ramsay. 2011. Renal lesions of non-domestic felids. Vet. Pathol. 48: 698–705.

2. Palmquist, R. 2006. A preliminary clinical evaluation of Kibow Biotics®, a probiotic agent, on feline azotemia. J. Am. Holistic Vet. Med. Assoc. 24: 23–27.

3. Ranganathan, N., E. A. Friedman, P. Tam, V. Rao, P. Ranganathan, and R. Dheer. 2009. Probiotic dietary supplementation in patients with stage 3 and 4 chronic kidney disease: a 6-month pilot scale trial in Canada. Curr. Med. Res. Opin. 25: 1919–1930.

4. Ranganathan, N., B. Patel, P. Ranganathan, J. Marczely, R. Dheer, T. Chordia, S. R. Dunn, and E. A. Friedman. 2005. Probiotic amelioration of azotemia in 5/6th nephrectomized Sprague-Dawley rats. Sci. World J. 5: 652–660.

5. Ranganathan, N., B. Patel, P. Ranganathan, J. Marczely, R. Dheer, T. Chordia, Z. Yang, and E. A. Friedman. 2005. Probiotic reduces azotemia in Gottingen minipigs. 3rd World Congress of Nephrology, Singapore (Abstr.).

6. Ranganathan, N., B. Patel, P. Ranganathan, J. Marczely, R. Dheer, B. Pechenyak, S. R. Dunn, W. Verstraete, K. Decroos, R. Mehta, and E. A. Friedman. 2006. In vitro and in vivo assessment of intraintestinal bacteriotherapy in chronic kidney disease. ASAIO J. 52: 70–79.

7. Ranganathan, N., P. Ranganathan, E. A. Friedman, A. Joseph, B. Delano, D. Goldfarb, P. Tam, A. V. Rao, E. Anteyi, and C. G. Musso. 2010. Pilot study of probiotic dietary supplementation for promoting healthy kidney function in patients with chronic kidney disease. Adv. Ther. 27: 634–647.

8. Simon, F., A. Romvary, and S. Mora. 1989. Clinical investigations of medetomidine in dogs. Acta Vet. Scand. Suppl. 85: 161–165.

9. Wack, R. F. 2008. Treatment of chronic renal failure in nondomestic felids. *In:* Fowler, M. E., and R. E. Miller (eds.). 2008. Zoo and Wild Animal Medicine, 6th ed. Elsevier, Philadelphia, Pennsylvania. Pp. 462–465.

Received for publication 9 December 2010