Serum Fructosamine in Cats Receiving an Oral Chondroprotective Agent

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ABSTRACT

This study was designed to examine the effects of glucosamine and chondroitin sulfate (Glu/CS) supplementation on serum fructosamine concentrations in healthy cats. Eight cats were enrolled; one cat was removed from the study after developing conjunctivitis. The remaining 7 cats were treated with oral Glu/CS once daily for three weeks, at the manufacturer's recommended dose. Serum fructosamine was measured on day 0 and day 22. The mean serum fructosamine concentrations remained within the reference range and there was no significant difference in serum fructosamine concentrations before and after Glu/CS supplementation (p=0.178). Thus oral Glu/CS supplementation does not significantly affect serum fructosamine concentrations in healthy cats when administered at standard recommended doses. These findings may improve the confidence of veterinarians in using these chondroprotective agents in cats with diabetes mellitus.

INTRODUCTION

Degenerative joint disease (DJD), also termed osteoarthritis, is a significant problem in small animal practice.[1] This disorder affects the quality of life of many cats, and can also affect the human-animal bond by interfering with activities, such as playing, that are enjoyed by pets and their owners. There are several non-surgical management strategies available for the management of DJD, including the use of corticosteroids, non-steroidal anti-inflammatory drugs, weight control, and physical therapy.[1,2]

Chondroprotective agents are widely used in both human and veterinary medicine in the management of DJD. One of the most frequently used medications in this class is the combination of glucosamine and chondroitin sulfate (Glu/CS).[2,3,4] Many clinicians have noted relief from joint pain in animals treated with Glu/CS,[1] and a recent randomized double-blind controlled clinical trial has demonstrated that Glu/CS has a positive clinical effect in dogs with osteoarthritis.[5]

Adverse effects of Glu/CS are extremely

rare, and in fact it is classified as non-toxic.[3] A study in 12 normal cats showed that oral administration of Glu/CS for 30 days, at twice the recommended dose, was associated with no clinically or statistically significant changes in hematologic, hemostatic, or biochemical variables. All of the cats remained healthy and showed no adverse reactions to treatment.[6] Glucosamine is 2-amino-2-deoxy-α-D-glucose, an amino monosaccharide derivative of glucose.[4] Intravenous administration of high doses of glucosamine has been shown to induce insulin resistance in experimental animals.[7] However studies in humans have shown that oral administration of standard doses of glucosamine does not cause or worsen insulin resistance in lean or obese subjects,[8] and Glu/CS supplementation in human diabetic patients does not result in clinically significant alterations in glycosylated hemoglobin levels.[9]

The term fructosamine refers to serum proteins, primarily albumin, that are irreversibly linked to a sugar, usually glucose, in a process termed glycation.[10,11] Fructosamine concentrations therefore reflect the average blood glucose concentrations over the life-span of the serum proteins that are glycated. In dogs and cats, serum fructosamine concentrations are considered to reflect the average blood glucose concentration during the preceding 2 to 3 weeks.[10-12] This time span is related to the half-life of plasma proteins; however, the exact half-life of plasma proteins in the cat is unknown.[13] Serum fructosamine is widely used in dogs and cats to diagnose diabetes mellitus, and to evaluate glycemic control in diabetic patients.[12,14,15] It is also useful for differentiating between diabetes mellitus and transient elevations in blood glucose concentrations due to stress.[16]

Despite the paucity of evidence for adverse effects of Glu/CS on diabetic regulation, veterinarians sometimes express concern about the potential impact of this therapy on the management of diabetic patients, and the effect of this therapy on the interpretation of serum fructosamine values. As the first step towards addressing these concerns, this study was designed to evaluate the effects of Glu/CS supplementation on serum fructosamine concentrations in healthy cats. The hypothesis was that Glu/CS supplementation has no effect on serum fructosamine concentrations.

MATERIALS AND METHODS

Study Participants

The study protocol was approved by the Colorado State University Institutional Animal Care and Use Committee. A total of 8 healthy, mixed-breed, 16-month-old, purpose-bred research cats were initially enrolled in the study. The group of cats included 5 spayed females and 3 neutered males, with body weights ranging from 3.6 to 7.1 kg. All cats received a full physical examination, serum chemistry profile, complete blood count (CBC) and urinalysis upon admission to the study. Cats exhibiting clinical signs of illness prior to or during the study were excluded.

Study Design

The results of a previous study of the effects of Glu/CS supplementation on serum fructosamine in dogs, performed by the author, were used to perform a power calculation.[17] Using the standard deviation found in this study (36 µmol/L), 7 cats were calculated to provide a power of 86% to detect a difference in serum fructosamine of 50 µmol/L, with an alpha of 0.05, using a paired Student's t-test. The value of 50 µmol/L was chosen as this would be regarded as clinically significant.[12] To allow for possible non-compliance, or withdrawal of study participants, a total of eight healthy research cats were initially enrolled in the study.

Oral Glu/CS (Cosequin for Cats®; Nutramax Laboratories Inc., Edgewood, MD) was administered once daily for 21 days. This product is supplied in a capsule form and contains a flavored powder, glucosamine hydrochloride (125mg), sodium chondroitin sulfate (100 mg) and manganese (1 mg). The product may be administered in a capsule

form orally or alternatively the capsule may be opened and the contents mixed with or sprinkled over food. In accordance with the manufacturer's recommendations for initial administration, cats of less than 10 lb (4.5 kg) body weight received one capsule once daily and cats of greater than 10 lb (4.5 kg) body weight received two capsules once daily. Based on the individual animal's compliance, cats were either directly pilled or ate the contents of the capsule sprinkled on highly palatable food (a/d®; Hill's Pet Nutrition, Inc.). The cats that received the medication in food were fed and observed individually to confirm that they consumed the entire contents of the capsule.

Sample Analysis

Serum fructosamine was measured on day 0, prior to Glu/CS administration, and day 22 at the Colorado State University Veterinary Medical Center Clinical Pathology Laboratory, using a colorimetric assay based on nitrotetrazolium-blue reduction. The reference range for feline serum fructosamine concentration at this laboratory is 150-325 µmol/L.

Statistical Analysis

A paired Student's t-test was performed to compare mean serum fructosamine concentration in cats before and after 21 days of Glu/CS supplementation. A p value less than 0.05 was considered to be statistically significant.

RESULTS

Eight cats were enrolled in this study. Initial physical examination, CBC, serum chemistry profile, and urinalysis were unremarkable in all cats. Shortly after beginning the study, one neutered male cat developed conjunctivitis that required antibiotic therapy. Due to the presence of illness, this cat was excluded from the data analysis. The remaining seven cats successfully completed the study and no adverse effects of Glu/CS supplementation were seen in any cat. Of the 7 cats, 5 consistently consumed the Glu/CS supplement in food, and 2 were consistently pilled. Table 1 summarizes the body weight, sex, mg/kg dose of glucosamine, method of Glu/CS administration, and serum fructosamine results for each cat.

The mean serum fructosamine concentrations before and after Glu/CS supplementation were 241.8 and 258.0 µmol/L respectively, with a mean increase of 16.2 µmol/L. All individual fructosamine concen-

Table 1: *Summary of research animal data including sex, weight, dose of glucosamine, method of Glu/CS administration, and serum fructosamine concentrations before and after Glu/CS supplementation.*

Cat #	Sex	Weight (kg)	Glu Dose (mg/kg)*	Administration Method	Pre-Glu/CS Fructosamine (µmol/L)	Post-Glu/CS Fructosamine (µmol/L)
1	MN	6.33	39.5	In food	285	268
2	FS	6.12	40.8	In food	298	301
3	FS	3.8	32.9	In food	204	219
4	FS	3.67	34.1	Pilled	215	256
5	FS	5.8	43.1	Pilled	170	230
6	MN	7.1	35.2	In food	276	263
7	FS	4.77	52.4	In food	245	269

*Abbreviations: MN = neutered male; FS = spayed female; Glu = glucosamine; Glu/CS = glucosamine/chondroitin sulfate. *Glucosamine dose was calculated based on the Glu content of the capsule (125 mg) and the manufacturer's recommended dose of 1 capsule for cats weighing less than 4.5 kg and 2 capsules for cats weighing greater than 4.5 kg.*

trations remained within normal reference limits (reference range: 150-325 µmol/L). The standard deviation of the fructosamine values before and after Glu/CS supplementation were 47.45 and 27.09 µmol/L respectively. A paired Student's t-test revealed no significant difference in serum fructosamine concentrations before and after Glu/CS supplementation (p=0.178).

DISCUSSION

Supplementation with Glu/CS is commonly recommended by veterinarians to help manage osteoarthritis in feline patients. The product is also widely used in other companion animals, and in humans.[3-5,18,19] Concern has been raised over the effects of Glu/CS on glucose metabolism in human patients with diabetes mellitus.[9] Glucosamine is a derivative of glucose, and one possible mechanism by which it could affect blood glucose levels is through conversion back to glucose. However the pathway for derivation of glucosamine from glucose is irreversible in humans.[9] The reversibility of this pathway in animals is unknown, but oral Glu/CS supplementation has been shown to have no effect on blood glucose levels in healthy cats or dogs.[6,20] An alternate mechanism by which glucosamine may affect glycemic control involves glucosamine and the hexosamine biosynthesis pathway.[9] In the hexosamine pathway, endogenous glucosamine is synthesized by the enzyme glutamine:fructose-6-phosphate amidotransferase (GFAT). This pathway appears to be activated when cellular glucose uptake is sufficient to meet energy requirements, leading to shunting of glucose to glucosamine synthesis, as well as down-regulation of glucose transport.[9] Studies in animal models have shown that over-expression of GFAT leads to insulin resistance and decreased glucose uptake by tissues.[21] It has been theorized that exogenous glucosamine could produce similar effects, signaling that cells have adequate glucose stores, with resultant decreased glucose transport, hyperglycemia, and insulin resistance.[9] However, many clinical trials have specifically investigated the effects of glucosamine supplementation in humans, and they have shown no evidence of adverse effects on glucose homeostasis.[22]

The results of the present study suggest that oral Glu/CS supplementation does not significantly affect serum fructosamine concentrations in healthy cats when administered at doses recommended by the manufacturer. These results are consistent with a previous study performed in healthy dogs receiving oral Glu/CS supplementation.[17] In a placebo-controlled, double-blinded, randomized clinical trial of human patients with diabetes mellitus, researchers found no clinically significant alterations in glucose metabolism in patients receiving Glu/CS supplementation, as assessed by the measurement of glycosylated hemoglobin levels.[9] The present study evaluated only healthy cats, and therefore does not provide direct information regarding the effects of Glu/CS supplementation in cats with diabetes mellitus. However the findings in humans with diabetes mellitus together with the present findings in normal cats suggest that altered fructosamine levels are unlikely to be a significant clinical concern in feline diabetic patients receiving Glu/CS. A study of the effects of Glu/CS supplementation on serum fructosamine concentrations in cats would require a large number of subjects, due to the marked variability in fructosamine levels in patients with diabetes mellitus. For example in diabetic cats, the standard deviation for serum fructosamine concentrations has been reported to be 140 µmol/L for a group of 12 well-controlled patients.[14] Using this value for standard deviation, a study of 64 cats would be necessary to provide a power of 80% for the detection of a 50 µmol/L change in serum fructosamine concentration using a paired Student's t-test.

A power calculation conducted prior to beginning this project was based on a standard deviation of 36.1µmol/L, from data in a previous canine study.17 This would have provided a power of 86% to detect a difference in serum fructosamine of 50 µmol/L.

The actual standard deviation in the present study was slightly higher than anticipated, thus this study may be slightly underpowered. However it is important to note that regardless of statistical significance, the difference between the mean serum fructosamine concentrations before and after Glu/CS supplementation was only 16.2 µmol/L. This value would be regarded as clinically insignificant. When fructosamine concentrations are used to monitor diabetic regulation, changes of approximately 50 µmol/L are considered to be clinically relevant. For example, glycemic control in a cat with diabetes mellitus would be regarded as excellent if serum fructosamine were 350 µmol/L, and good if the value were 400 µmol/L.[12]

It has recently been reported that the critical difference for fructosamine values in cats is 33 µmol/L.[13] The significance of this value is that if two consecutive measurements on different days are less than the critical difference, then the change between the different days is due to random variation and is not significant. In the present study, the mean change in fructosamine was markedly less than this critical difference, again confirming that this change in unlikely to be clinically significant. However, upon examining the values from individual cats it is apparent that the change in serum fructosamine concentration exceeded the critical difference in 2 animals. In cat #4 and cat #5 the serum fructosamine concentrations increased by 41 µmol/L and 60 µmol/L respectively, after Glu/CS supplementation. It is interesting to note that these were the 2 cats that were required consistent daily pilling for administration of the Glu/CS. Cat #5 was particularly fractious and resisted handling. The remaining 5 cats readily ate the Glu/CS supplement when it was sprinkled on food. Pilling required a minimal amount of physical restraint applied to the individual cat and likely produced a variable amount of psychological stress, anxiety, or fear for the animal.

Stress is a recognized cause of hyperglycemia in cats.[12,16,23] One study found a strong relationship between increased glucose concentration and struggling associated with short-term physical restraint.[23] In theory serum fructosamine levels should not be affected by acute increases in blood glucose concentration that occur with stress or excitement induced hyperglycemia;[12] however, it is plausible that repeated, small stressful events such as pilling, may cause a daily stress induced hyperglycemia resulting in elevated serum fructosamine concentrations. Additionally, poorly socialized cats or cats unaccustomed to routine handling procedures, such as a population of research cats, may react differently to minor stressors such as physical restraint.[23] In hindsight, a placebo-controlled study would have been helpful to eliminate or minimize the effect of stress as a potential variable in this study. Further investigation is needed to determine the effect of daily stressors on serum fructosamine concentrations in cats.

CONCLUSION

This results of this study show that Glu/CS supplementation has no effect on serum fructosamine concentrations in healthy cats, when administered at doses recommended by the manufacturer. These findings may help decrease concerns about the effects of Glu/CS on glucose regulation in diabetic cats and improve the confidence of veterinarians in using these chondroprotective agents in these patients. However, further studies using a larger sample size with a placebo control would provide definitive evidence regarding the effects of Glu/CS on glycemic control in diabetic cats. The results of the present study do not preclude the need for regular blood glucose monitoring in diabetic cats receiving Glu/CS supplementation.

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