

Effects of a Glucagon-like Peptide-1 Mimetic (Exenatide) in Healthy Cats

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ABSTRACT

To determine the insulinotropic effects of an incretin mimetic, exenatide, a hyperglycemic clamp was used to evaluate three different doses (0.1, 0.24, and 1 $\mu\text{g}/\text{kg}$) administered subcutaneously to healthy cats. Subsequently, drug safety during chronic administration was evaluated during 4 weeks of twice daily exenatide treatment.

Administration of exenatide at the highest dose tested, 1 $\mu\text{g}/\text{kg}$, increased plasma insulin concentration during hyperglycemia from 15 to 120, and also at 240 minutes post administration, as compared to a saline control. Exenatide at lower doses (0.1 and

0.24 $\mu\text{g}/\text{kg}$) had lesser effects on plasma insulin concentrations, thus insulin release was stimulated in a dose-dependent manner. Chronic administration of 1 $\mu\text{g}/\text{kg}$ exenatide did not lead to apparent adverse effects, but significant weight loss was observed in cats during this period.

Exenatide's insulinotropic action combined with its safety profile in healthy cats suggests that study in diabetic cats is warranted.

INTRODUCTION

Diabetes mellitus is a common feline endocrinopathy. Diabetes in cats is associated with a progressive loss of beta cell function in the pancreatic islet cells as a result of compensatory hyperinsulinemia stimulated

by glucose intolerance and insulin resistance.¹ The pathophysiology of the disease in felines closely resembles type II diabetes mellitus (T2DM) in humans, and stages of beta cell failure in cats with experimentally-induced diabetes are similar to those of humans with T2DM.² In human T2DM there is an accumulation of amyloid in the pancreatic beta cells, contributing to beta cell loss. Humans, cats, raccoons, and non-human primates are the only species known to form pancreatic amyloid deposits as a feature of spontaneously occurring diabetes mellitus. Cats may, therefore, be a uniquely appropriate model for human T2DM.³

One of the most promising new directions in T2DM therapy in people involves manipulation of the “incretin effect.” This refers to the phenomenon in which orally ingested glucose leads to a greater insulin response compared to an equimolar amount of intravenously administered glucose.⁴ Gastrointestinal hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide (GIP) are responsible for this effect in healthy individuals. These incretin hormones enhance glucose-dependent or meal-stimulated insulin production and secretion from the pancreatic beta cells in response to intraluminal nutrients, primarily glucose, in the gastrointestinal tract.⁵ Thus, they serve to suppress post-prandial hyperglycemia. Sensitivity of people with T2DM to this effect mediated by GIP is decreased, though response to GLP-1 is preserved.⁶ Therefore, recent therapeutic interventions have focused on manipulation of GLP-1. Additional beneficial actions of GLP-1 in people include suppression of glucagon release, delay of gastric emptying, and suppression of appetite.⁷

Exenatide (Byetta, TM Lilly) is a synthetic form of the naturally-occurring peptide exendin-4, which is isolated from the salivary gland of the Gila monster (*Hemidactylus* *suspectum*).⁸ It is a GLP-1 mimetic that has a longer circulating half-life and greater affinity for the GLP-1 receptor than

the native hormone, as well as enhanced resistance to the enzyme dipeptidyl peptidase-4 (DPP-4) which degrades GLP-1.⁹ Studies in T2DM patients have demonstrated its efficacy in improvement of glycemic control and promotion of weight loss both as an add-on therapy to routinely used oral hypoglycemic agents¹⁰ and as a monotherapy.¹¹ It also performed favorably when compared to insulin glargine as an add-on therapy in inadequately controlled T2DM patients receiving oral hypoglycemic agents with exenatide-treated patients experiencing similar improvements in glycemic control and more weight loss compared to patients receiving insulin.¹² Exenatide has been shown to restore first-phase insulin release in T2DM patients to that experienced by healthy subjects.¹³

Since T2DM in people and cats share pathophysiologic features, an incretin mimetic such as exenatide could eventually prove useful for the management of diabetic cats as well. The primary objective of this research was to discern the effect of a single administration of exenatide on insulin secretion in healthy cats during induced hyperglycemia. In addition, the safety of chronic administration was assessed.

MATERIALS AND METHODS

Animals

Study protocol and animal treatment were reviewed and approved by the Oklahoma State University Animal Care and Use Committee in compliance with federal guidelines. Nine healthy cats (four male and five female), 2 to 8 years of age initially ranging from 2.7 to 7.1 kg, were included in the study. Initial health status was confirmed through physical examination, complete blood count, serum biochemical analysis, serum fructosamine, fecal flotation and smear, urinalysis, and FIV/FeLV testing.^b Cats were surgically sterilized, then allowed 4 weeks for acclimation prior to the studies. They were individually housed in a common location and provided an adult maintenance diet twice daily (canned, dry, or a mixture fed based on cat preference) and water ad

libitum. Cats were fed to maintain initial body weights based on the recommendations of the label of the diet(s) fed. Light cycles were at 12-hour intervals. Cats were allowed periods of environmental enrichment throughout the study.

Study 1: Hyperglycemic

Clamp/Dose-Determination

A hyperglycemic clamp was performed on six cats (three males, three females) in order to simulate a hyperglycemic state such as that found in T2DM. The hyperglycemic clamp is cited as the preferred technique for assessing response of beta cells to glucose.¹⁴ Each cat underwent this procedure on four separate occasions (3 doses of exenatide and a saline control) over a course of 30 days. All cats received each of the exenatide doses and the saline control in a randomized fashion with a minimum of 48 hours between each treatment.

Cats were fasted overnight prior to catheter placement. Tiletamine/zolazepam (Telazol; Fort Dodge)d was administered at a dose of 6-10 mg/kg IM. A 5 Fr, 8 cm double-lumen jugular catheter and a 20 or 22 gauge 1” cephalic catheter were placed in a sterile manner. The catheters were flushed with heparinized saline (1 unit/ml) every 8 hours to maintain patency and covered with bandaging material. Soft e-collars were kept in place. Each cat underwent placement of a jugular catheter on two separate occasions within the 1 month period.

After an overnight fast, a hyperglycemic clamp was performed using a 20% dextrose solution (50% dextrose stock solution diluted with saline) infused through the cephalic catheter as described previously¹⁴ to maintain the blood glucose between 160 and 200 mg/dL. Glucose concentration was determined at 5-15 minute intervals throughout the hyperglycemic clamp using blood drawn from the jugular catheter evaluated with a hand-held glucometer.e Once the dextrose infusion rate needed to maintain the desired blood glucose concentration remained constant for 30 minutes, exenatide (0.1 µg/kg, 0.24 µg/kg, or 1 µg/kg) or saline was

administered subcutaneously. Exenatide (250 µg/ml) was withdrawn aseptically from the injection pen and diluted 1:10 to 1:100 with saline to facilitate administration. The volume of saline administered for the control treatment was the same as the volume of the diluted exenatide at the 1 µg/kg dose for each cat. Blood samples were collected from the jugular catheter for insulin measurements at times -10 and -5 minutes (prior to treatment) and 0, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment using a 3-syringe sampling technique, with between 0.8 and 1 ml of blood drawn at each assay time.

Insulin Assay

Whole blood samples were collected in sodium heparin tubes and immediately placed in an ice bath. Samples were centrifuged within 4 hours of collection and the plasma stored at -80 °C until assayed. Insulin was measured by a radioimmunoassayf previously validated for use in cats.¹⁵ Assay performance was confirmed in our laboratory by demonstrating linearity, parallelism, and intraassay precision. Serial dilution of a cat plasma sample with high endogenous insulin concentration resulted in a curve similar to that of the standards with an r²= 0.99. Intraassay variation was 5.4% at 37 µIU/ml (n=8 replicates) and 5.3% at 120 µIU/ml (n=10 replicates). All samples were run in duplicate, and all samples from an individual animal from a single dose experiment were run in the same assay.

Study 2:– Chronic Exenatide

Administration

The safety of exenatide for chronic use was evaluated in nine cats total (including the six cats that were part of Study 1). A complete blood count, serum biochemical analysis, serum fructosamine, and feline pancreatic lipase immunoreactivity (PLI) test were performed at days 0 and 28 of the chronic administration period. Exenatide was administered at 1 µg/kg subcutaneously (diluted 1:10 with saline; new dilution for every administration) every 12 hours for 28 days based on each cat’s weight at the

beginning of Study 2. During this time, the cats were monitored twice daily for adverse effects, such as inappetence, vomiting, and diarrhea. Body weights were measured weekly throughout the chronic administration period as well as during the 26 days prior to this study.

STATISTICS

The area under the plasma insulin concentration versus time curve (AUC) was determined as the sum of linear trapezoids from the time of drug administration through the approximate duration of action of the highest dose of exenatide. This insulin AUC was used to visualize insulin release as a function of dose of exenatide administered. Percent change in body weight with chronic exenatide administration was calculated by dividing the change in body weight for a given period of time by the initial body weight at the start of the time period and multiplying by 100. Mean body weight \pm SD of all cats was calculated at days -26, 0, and 28 of the chronic administration period. All statistical analyses were conducted with PC SAS Version 9.2.g Analysis of variance procedures with a repeated measures model (PROC MIXED) were utilized to assess the combined effects of treatment group and time since treatment on plasma insulin concentration, dextrose infusion rate, and plasma glucose concentration. An autoregressive period 1 covariance structure was utilized to model the within cat variance-covariance structure. The simple effects means and standard errors of the groups, given time, were reported and assessed with a SLICE option in an LSMEANS statement. When overall simple effects were deemed

significant, pair-wise t tests were performed with a DIFF option to further assess the group differences. Body weight change was assessed by a one-way repeated measure ANOVA. A significance level of 0.05 was used for all comparisons.

RESULTS

Exenatide at doses of 0.24 and 1 μ g/kg resulted in an increase in plasma insulin concentration in cats during hyperglycemic clamp testing with a mean onset of insulinotropic action at 15 minutes and a duration of action of 90 minutes (0.24 μ g/kg dose) or 120 minutes (1 μ g/kg dose). For both the 0.24 and 1 μ g/kg doses, a second insulin peak was observed at 240 minutes. Following exenatide administration, the plasma insulin concentrations were significantly ($P < 0.05$) elevated as compared to saline control from 15 to 120 minutes and at 240 minutes after a dose of 1 μ g/kg of exenatide and from 15 to 90 minutes and at 240 minutes after a dose of 0.24 μ g/kg of exenatide (Figure 1). When the insulin AUC from 0-120 minutes was determined for each cat, exenatide administration increased insulin release in a dose-dependent manner during experimentally induced hyperglycemia (Figure 2). Exenatide appeared to conform to a typical logarithmic Emax dose-response model with no or minimal insulinotropic effect at the lowest dose tested (0.1 μ g/kg), but the maximum effect was undefined by the range of utilized doses (Figure 2). Neither blood glucose concentration nor dextrose infusion rate differed at any time point between the four treatment groups (Figure 3).

Chronic administration of exenatide did not result in any clinical or hematologic ab-

Table 1: Mean weight \pm SD of 9 cats prior to treatment (days 0 and -26) and after 28 days of exenatide treatment at 1 μ g/kg. Mean percentage change in weight \pm SD during 26 days prior to and after 28 days of exenatide treatment.

	Weight @ Day -26 (kg)	Weight @ Treatment Onset Day 0 (kg)	Weight @ Treatment End Day 28 (kg)	% Weight Change Pre-Treatment (days -26 to 0)	% Weight Change Post-Treatment (days 0 to 28)
Mean \pm SD	4.74 \pm 1.4	4.78 \pm 1.5	4.48 \pm 1.5	0.6 \pm 2.2	-7.0 \pm 4.9

Figure 1: Insulin increase after administration of a single subcutaneous dose of exenatide during hyperglycemic clamp in 6 healthy cats. Each cat received each of three doses of exenatide and a saline control. * significantly different from saline control ($p < 0.05$)

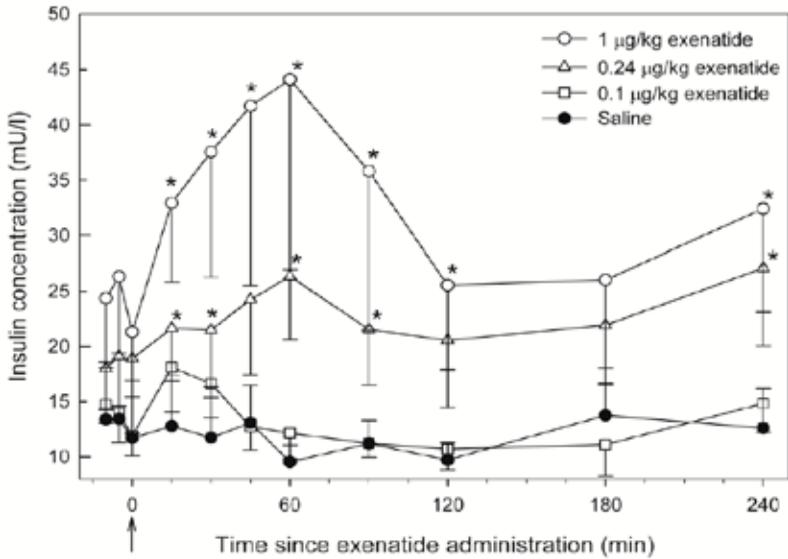


Figure 2: Dose-response curve of insulin increase as a function of a single subcutaneous dose of exenatide in 6 healthy cats. The area under the curve was calculated for the insulin concentration from 0 to 120 minutes after the subcutaneous administration of exenatide over a range of dose rates.

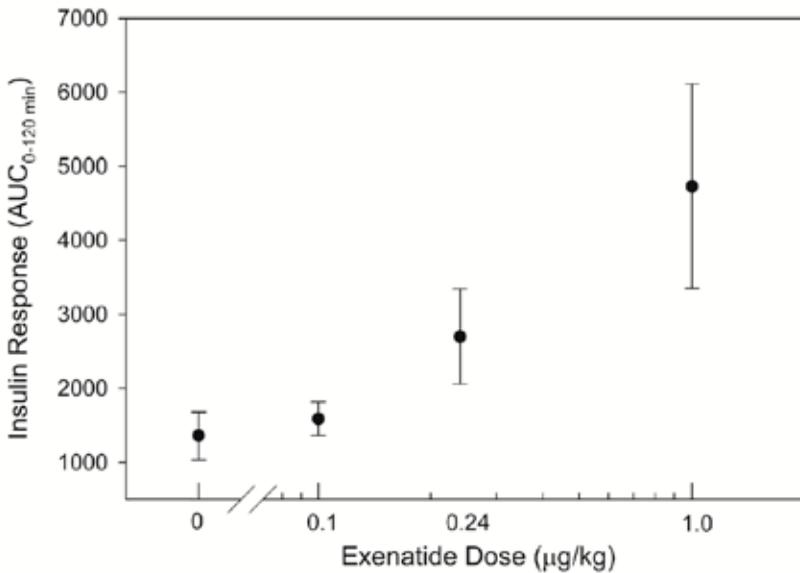
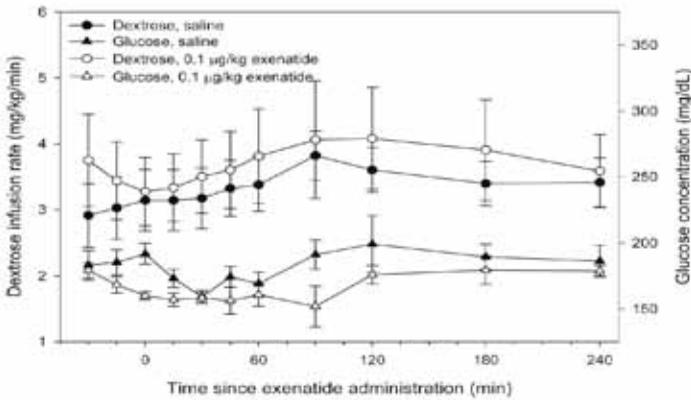
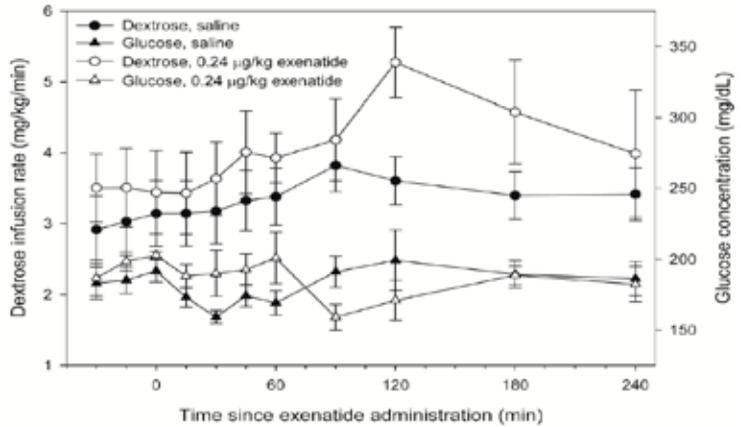


Figure 3: Dextrose infusion rate and glucose concentration over time for various doses of exenatide compared to a saline control during hyperglycemic clamp in 6 healthy cats.

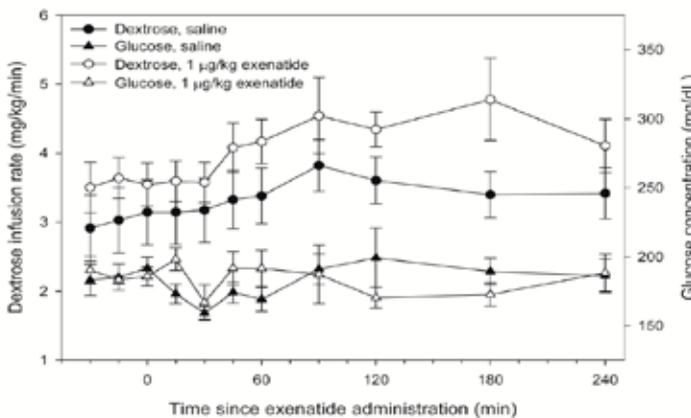
(A) 0.1 µg/kg dose



(B) 0.24 µg/kg dose



(C) 1 µg/kg dose



normalities (no significant abnormalities in values on days 0 and 28) other than a slight increase in serum PLI in one cat, which persisted when reevaluated 14 days after chronic drug administration was completed (serum PLI: day 0 = 1.5 $\mu\text{g/L}$, day 28 = 4.1 $\mu\text{g/L}$, day 14 post-study = 4.5 $\mu\text{g/L}$; normal <3.5 $\mu\text{g/L}$). Body weights for the cats in the chronic exenatide administration study decreased throughout the period of administration (Table 1). Weights for days 7, 14, 21, and 28 of the administration period were significantly lower than at day 0. In contrast, there was no significant change in body weight in the 26 days prior to onset of chronic exenatide administration (Table 1).

DISCUSSION

The results of the current study reveal an insulinotropic effect of exenatide administered subcutaneously to healthy cats with induced hyperglycemia, which also occurs in healthy people under similar conditions of induced hyperglycemia.⁹ Exenatide has been used successfully for several years in the treatment of T2DM in people.¹⁰ Based on the results of the current study, evaluation of the drug's effects in diabetic cats is warranted.

Exenatide, a synthetic GLP-1 (an incretin hormone) mimetic, causes pancreatic production and release of pre-packaged insulin in response to increased nutrient content in the lumen of the intestinal tract. The purported advantage of exenatide compared to traditional T2DM therapies, such as exogenous insulin or oral hypoglycemic treatment, is that it is active only during hyperglycemia. Once euglycemia is restored, exenatide ceases to stimulate insulin secretion in people,¹⁶ thereby theoretically avoiding the detrimental effects of hypoglycemia that can occur with other types of therapy. Counter-regulatory capacity following exenatide administration during periods of induced hypoglycemia in healthy people is not only intact, but enhanced. A lack of insulinotropic action as well as increased glucagon levels have been found in hypoglycemic people receiving exenatide compared to subjects receiving a placebo.¹⁶

We can conclude that insulin concentration increased as a result of the drug effect rather than secondary to administration of excess dextrose solution during the hyperglycemic clamp procedure, as blood glucose concentrations did not vary significantly between groups during the hyperglycemic clamp testing (Figure 3). Dextrose infusion rates tended to increase slightly during the course of the study period in all cats, especially after exenatide administration. However, the dextrose infusion rate necessary to maintain the desired hyperglycemia during the clamp did not differ significantly between treatment groups despite a dose-dependent increase in serum insulin concentration. A dissociation between insulin concentration and dextrose infusion rate following drug administration was also observed in a recent report of exenatide administration in healthy cats,¹⁷ suggesting that this is most likely a physiological event, rather than a lack of statistical power. Exenatide may have non-insulinotropic effects on glucose levels in cats that are as yet undefined, thus requiring further study.

In humans, with T2DM, exenatide at both 0.1 and 0.2 $\mu\text{g/kg}$ caused a dose-dependent insulin increase that lasted for 180-240 minutes.¹⁸ The duration of significant insulinotropic action of the 1 $\mu\text{g/kg}$ exenatide dose in healthy cats was approximately 120 minutes in the present study. Interestingly, although the study designs differed sufficiently to preclude direct comparison, Gilor et al also observed a short duration of insulinotropic action using exenatide.¹⁷ Unexpectedly, a second rise in insulin concentration occurred in our cats at 240 minutes at both the 0.24 and 1 $\mu\text{g/kg}$ doses. This may have resulted from insulin release independent of drug effect, possibly due to diurnal variation or environmental factors evoking stress or excitement. However, this late increase in plasma insulin could also indicate an exenatide-induced biphasic pattern of insulin secretion. Further studies that include later sampling time points are needed to clarify the significance of a possible biphasic insulinotropic response to

exenatide administration.

When administered to T2DM patients, exenatide has been shown to suppress glucagon release, delay gastric emptying to increase feelings of satiety, and decrease appetite through its action as a neurotransmitter in the hypothalamus.⁸ Increased central and peripheral satiety serves to decrease caloric consumption and promote weight loss. This is advantageous in T2DM treatment as obesity leads to worsening of many important parameters in diabetic patients, including glycemic control, lipid levels, and blood pressure.¹⁹ Unfortunately, many of the traditional medications used to manage T2DM lead to weight gain, inciting a vicious cycle.²⁰ Diabetic cats can also suffer from obesity,³ which is an important contributory factor to pathogenesis of the disease, making this a pertinent consideration in veterinary medicine as well.

In the current study, cats demonstrated body weight loss by one week after beginning daily administration of exenatide, with continued weight loss until the end of the study (day 28). During the acclimation period, cats were fed to maintain their weights and this predetermined quantity of food was offered during the chronic administration phase. Cats had not experienced significant changes in body weight during the 26-day period prior to the chronic administration study (Table 1). Unfortunately, the cats' food intake and body condition scores were not quantified since the weight loss was an incidental finding and not an anticipated outcome. Therefore, although no concurrent adverse gastrointestinal signs were observed, it remains unknown if cats receiving exenatide experienced weight loss due to increased satiety as is observed in people.²¹ Although weight loss would be of benefit for obese diabetic cats, weight loss in diabetic cats of average to below average body condition may not be a desirable outcome. Further work is needed to elucidate the safety of exenatide in the non-obese diabetic cat.

The most common adverse effect reported with exenatide use in humans is

nausea, which is usually dose-dependent, temporary, and self-limiting.²² Concerns with T2DM patients experiencing pancreatitis while receiving exenatide therapy have surfaced. The majority of these patients had concurrent known risk factors for pancreatitis such as obesity, dyslipidemia, or alcohol use, complicating the assessment of exenatide administration as the main cause of pancreatitis.^{23,24} Based on this information, we included feline pancreatic lipase immunoreactivity in our screening panel used to assess the safety of chronic exenatide administration. The single cat that demonstrated a slight PLI elevation did not experience any adverse clinical signs that could be associated with pancreatitis. Also, the PLI value was only slightly higher than the reference range, and persisted at about the same level two weeks after cessation of exenatide administration. Therefore, this small increase in PLI was of questionable clinical significance in the current study. However, further monitoring for this potential adverse effect would be warranted in any future studies. None of the cats displayed any significant adverse effects to the drug such as vomiting or inappetence. Based on these findings, administration of 1 µg/kg of exenatide subcutaneously every 12 hours to healthy cats was well-tolerated. It is unclear whether this would be true when used to treat diabetic cats or in cats receiving a higher dose of exenatide.

CONCLUSION

In conclusion, exenatide at doses of 0.24 µg/kg and 1 µg/kg increased endogenous plasma insulin concentrations when given as a single subcutaneous dose during a period of hyperglycemia. In addition, we found that chronic exenatide administration was associated with significant weight loss without overt adverse effects when given twice daily for 28 days. Exenatide has improved the management of human T2DM due to a variety of beneficial actions, including improvement in glycemic control and promotion of weight loss. The results obtained in the present study on the safety and endocrine

effects of exenatide suggest that cats may similarly benefit from the inclusion of this drug in the pharmacological management of diabetes, although further evaluation is needed to reach any definitive conclusions. Improved management of diabetes would decrease reliance on traditional therapies and improve the long-term outcomes of these patients. Since 1 µg/kg of exenatide was the highest dose studied, it is not presently known whether higher doses would have greater efficacy or duration of action while maintaining acceptable safety.

FOOTNOTES

- a Exenatide, Lilly, Indianapolis, IN
- b SNAP® FIV/FeLV Combo, IDEXX Laboratories, Inc., Westbrook, ME
- c Hill’s Feline Adult Maintenance dry and canned foods, Hill’s Pet Nutrition, Inc., Topeka, KS
- d Tiletamine/zolazepam, Fort Dodge, Fort Dodge, IA
- e AlphaTrak, Abbott, Chicago, IL
- f Coat-a-Count, Siemens Medical Solutions Diagnostics, Los Angeles, CA
- g SAS Institute, Cary, NC

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REFERENCES

- 1 Rand J. Current understanding of feline diabetes: part 1, pathogenesis. *J Feline Med Surg* 1999; 1: 143-153.
- 2 Hoening M, Hall G, Ferguson D, et al. A feline model of experimentally induced islet amyloidosis. *Am J Pathol* 2000; 157: 2143-2150.
- 3 Hoening M. The cat as a model for human nutrition and disease. *Curr Opin Clin Nutr Metab Care* 2006; 9: 584-588.
- 4 Moore B, Edie ES, Abram JH. On the treatment of diabetes mellitus by acid extract of duodenal mucous membrane. *Biochem J* 1906; 1: 28-38.
- 5 Tolhurst G, Reimann F, Gribble FM. Nutritional regulation of glucagon-like peptide-1 secretion. *J Physiol* 2009; 587: 27-32.
- 6 Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide-1 [7-36 Amide] but not

- of synthetic human gastric inhibitory polypeptide in patients with type 2 diabetes mellitus. *J Clin Invest* 1993; 91: 301-307.
- 7 Nauck MA. Unraveling the science of incretin biology. *Eur J Intern Med* 2009; 20: S303-S308.
- 8 Gallwitz B. New therapeutic strategies for the treatment of type 2 diabetes mellitus based on incretins. *Rev Diabet Stud* 2005; 2: 61-69.
- 9 Egan JM, Cloquet AR, Elahi D. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. *J Clin Endocrinol Metab* 2002; 87: 1282-1290.
- 10 Buse JB, Klonoff DC, Nielsen LL, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clin Ther* 2007; 29: 139-153.
- 11 Nelson P, Poon T, Guan X, Schnabel C, Wintle M, Fineman M. The incretin mimetic exenatide as a monotherapy in patients with type 2 diabetes. *Diabetes Technol Ther* 2007; 9: 317-326.
- 12 Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widell MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes. *Ann Intern Med* 2005; 143: 559-569.
- 13 Fehse F, Trautmann M, Holst JJ, et al. Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 2005; 90: 5991-5997.
- 14 Slingerland LI, Robben JH, van Haefen TW, Kooistra HS, Rijnberk A. Insulin sensitivity and beta-cell function in healthy cats: assessment with the use of the hyperglycemic glucose clamp. *Horm Metab Res* 2007; 39: 341-346.
- 15 Lutz TA, Rand JS. Comparison of five commercial radioimmunoassay kits for the measurement of feline insulin. *Res Vet Sci* 1993; 55: 64-69.
- 16 Degn KB, Brock B, Juhl CB, et al. Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia. *Diabetes* 2004; 53: 2397-2403.
- 17 Gilor C, Graves TK, Gilor S, Ridge TK, Rick M. The GLP-1 mimetic exenatide potentiates insulin secretion in healthy cats. *Domest Anim Endocrinol* 2011; 41: 42-49.
- 18 Kolterman OG, Buse JB, Fineman MS, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 2003; 88: 3082-3089.
- 19 Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. *Endocrinol Metab Clin North Am* 2003; 32: 805-822.
- 20 DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131: 281-303.
- 21 Edwards CMB, Stanley SA, Davis R, et al. Exen-

- din-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 2001; 281: E155-E161.
- 22 Poon T, Neslson P, Shen L, et al. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. *Diabetes Technol Ther* 2005; 7: 467-477.
- 23 Denker PS, DiMarco PE. Exenatide (exendin-4)-induced pancreatitis. *Diabetes Care* 2006; 29: 471.
- 24 Cure P, Pileggi A, Alejandro R. Exenatide and rare adverse events. *N Engl J Med* 2008; 358: 1969-1971.

Conflict of Interest Statement

None of the authors of this paper have a conflict of interest to disclose.