Effect of the glucagon-like peptide-1 analogue exenatide extended-release in cats with newly diagnosed diabetes mellitus

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Abstract: Hintergrund: Exenatide extended-release ist ein Glukagon-ähnliches Peptid-1 Analogon, welches in der Humanmedizin bei Typ-2 Diabetes mellitus eingesetzt wird. Es erhöht die Insulinsekretion, inhibiert die Glukagonsekretion und erhöht das Sättigungsgefühl. In Untersuchungen an gesunden Katzen zeigte Exenatide extended-release wenig Nebenwirkungen und erhöhte die Insulinfreisetzung. Ziel: Das Ziel der Studie war es zu untersuchen, ob die zusätzliche Verabreichung von Exenatide extended-release zu Insulin und einer kohlenhydratarmen Diät bei Katzen mit neu- diagnostiziertem Diabetes mellitus zu einer Verbesserung der metabolischen Kontrolle und der Remission führt und welche Auswirkungen es auf das Körpergewicht hat. Tiere: Es wurden 30 Katzen mit neu-diagnostiziertem Diabetes mellitus in die Studie eingeschlossen. Methoden: Es handelt sich um eine prospektive, Placebo-kontrollierte Studie. Die Katzen wurden nach dem Zufallsprinzip zwei Gruppen zugeteilt. Eine Gruppe erhielt Exenatide extended-release, die andere 0.9%-ige Kochsalzlösung, jeweils einmal wöchentlich als subkutane Injektion. Die Katzen beider Gruppen erhielten zudem Insulin Glargin, sowie eine kohlenhydratarme Diät. Exenatide extended-release oder Placebo wurde über einen Zeitraum von 16 Wochen verabreicht, im Falle einer Remission wurden die Präparate für weitere 4 Wochen nach Absetzten des Insulins gegeben. Eine Blutglukosekonzentration innerhalb des Referenzbereiches, während mehr als vier Wochen nach Absetzten des Insulins, wurde als Remission definiert. Die Daten wurden mit nicht-parametrischen Tests ausgewertet. Resultate: Katzen, die mit Exenatide extended-release behandelt wurden, zeigten häufig einen vorübergehenden Appetitverlust (60% versus 20% in der Placebo-Gruppe) und Vomitus (53.3% versus 40.0%). In der Placebo-Gruppe wurde eine Gewichtszunahme beobachtet (P=0.002), während dies in der Exenatide extended-release-Gruppe nicht zu verzeichnen war. Eine Remission und eine gute metabolische Kontrolle wurden bei 40.0% bzw. bei 88.9% der Katzen in der Exenatide extended-release-Gruppe und bei 20.0% bzw. 58.3% der Placebo-Gruppe erreicht. Schlussfolgerung und klinische Anwendbarkeit–Die Anwendung von Exenatide extended- release bei Katzen mit Diabetes mellitus erwies sich als nebenwirkungsarm und es kam zu keiner signifikanten Gewichtszunahme. Die Daten weisen darauf hin, dass Exenatide extended-release die Remissionsrate und die metabolische Kontrolle verbessert, jedoch sind weitere Studien mit einer grösseren Anzahl an Katzen erforderlich, um diese zu bestätigen.

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EFFECT OF THE GLUCAGON-LIKE PEPTIDE-1 ANALOGUE EXENATIDE EXTENDED-RELEASE IN CATS WITH NEWLY DIAGNOSED DIABETES MELLITUS

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EFFECT OF THE GLUCAGON-LIKE PEPTIDE-1 ANALOGUE EXENATIDE EXTENDED-RELEASE IN CATS WITH NEWLY DIAGNOSED DIABETES MELLITUS

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Short title: exenatide extended-release in diabetic cats.

Key Words: feline, remission, metabolic control, incretin, treatment.

Abbreviations: DM, diabetes mellitus; exenatide-ER, exenatide extended-release; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; IGF-1, insulin-like growth factor 1; T4, thyroxine; Spec fPL, feline pancreatic lipase; DGGR, 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylres-orufin) ester; BCS, body condition score.

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The study was performed at the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Switzerland, and at the Department of Veterinary Medical Sciences, University of Bologna, Italy.

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Abstract

Background–Exenatide extended-release (-ER) is a glucagon-like peptide-1 analogue that increases insulin secretion, inhibits glucagon secretion and induces satiation in humans with type 2 diabetes mellitus. The use of exenatide-ER is safe and stimulates insulin secretion in healthy cats.

Objectives–To assess the safety of exenatide-ER and its effect on body weight, remission and metabolic control in diabetic cats receiving insulin and a low-carbohydrate diet.

Animals–Thirty client-owned cats with newly diagnosed diabetes mellitus.

Methods–Prospective placebo-controlled clinical trial. Cats were alternately allocated to receive exenatide-ER or 0.9% saline, administered subcutaneously, once per week. Both groups were treated with insulin glargine and received a low-carbohydrate diet. Exenatide-ER was administered for 16 weeks, or in cats that achieved remission it was given for 4 weeks after discontinuing insulin therapy. Remission was defined as euglycemia ≥4 weeks after discontinuing insulin therapy. Nonparametric tests were used for statistical analysis.

Results–Cats treated with exenatide-ER had transient adverse signs that included reduced appetite (60% vs. 20% in controls) and vomiting (53.3% vs. 40%). Body weight increased significantly in the placebo group (P=0.002), but not in cats receiving exenatide-ER. Cats treated with exenatide-ER achieved remission or good metabolic control in 40% or 88.9%, respectively, whereas in the control cats the percentage were 20% or 58.3% (P=0.427 and P=0.178, respectively).

Conclusion and clinical importance–Exenatide-ER is safe in diabetic cats, does not result in weight gain and may improve the rate of remission and metabolic control, although further studies in large cohorts are required.

Incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), have been the focus of recent studies because of their beneficial role in glucose homeostasis. Incretins are gastrointestinal hormones released in response to food intake that increase insulin secretion in various species and has shown to stimulate pancreatic β-cell proliferation in rodents.[1,2] Additionally, they inhibit glucagon secretion, slow gastric emptying, induce satiation and promote weight loss.[2] However, the half-life of GLP-1 and GIP is only a few minutes because they are rapidly cleaved by dipeptidylpeptidase-4 (DPP-4).[2,3] Incretin-based therapies have been developed for humans with type 2 DM; they include GLP-1 receptor analogues that are resistant to rapid degradation of DPP-4, such as liraglutide and exenatide or exenatide-ER, and DPP-4 inhibitors, such as sitagliptin and vildagliptin, which reduce the degradation of endogenous GLP-1. Exenatide-ER, which requires only once weekly dosing in human type 2 diabetic patients, was more efficacious in reducing glycated hemoglobin, improved metabolic control and promoted weight loss more often than DPP-4 inhibitors.[4] Exenatide-ER resulted in greater improvements in metabolic control, induced nausea and vomiting less frequently than exenatide which has to be given twice daily, although injection site irritations were more common.[5,6] Furthermore, exenatide-ER is currently considered an effective second-line treatment in humans with type 2 DM because it rarely induces hypoglycemia when used as monotherapy.[4-6]

To date, the biology and effects of incretins have been investigated only in healthy cats. In one study, GLP-1 increased after oral glucose administration.[7] DPP-4 inhibitors were shown to lower plasma glucagon and to enhance insulin secretion in cats.[8,9] Administration of exenatide, exenatide-ER or liraglutide resulted in glucose-dependent insulin secretion and a pronounced effect on insulin secretion during normoglycemia, and a reduction in body weight occurred after the administration of exenatide and liraglutide in cats.[10-13] A recent comparison of incretin-based

treatments in cats showed that exenatide and exenatide-ER have more pronounced effects on insulin secretion than sitagliptin (a DPP-4 inhibitor).[14] Furthermore, exenatide-ER was considered a better option than exenatide or sitagliptin because it is administered only once weekly and has fewer side effects.[14]

The goal of the present study was to determine whether administration of exenatide-ER is safe in newly diagnosed diabetic cats treated with insulin glargine and a low-carbohydrate diet. In addition, the effect of exenatide-ER on body weight, remission rate and metabolic control were investigated.

Materials and Methods

Animals

This prospective clinical trial used newly diagnosed diabetic cats admitted from January 2013 to January 2015. The diagnosis of DM was based on clinical signs and laboratory tests.[15] Cats were excluded if they had received insulin or other antidiabetic medication for longer than 4 weeks before admission, if glucocorticoids or progestagens had been given during the previous 3 months or if a concurrent disease such as e.g. renal failure, gastrointestinal disorder, heart disease, an other endocrinopathy or neoplasia was diagnosed. Diabetic cats with ketoacidosis or pancreatitis were included in the study if clinical signs resolved and their general condition improved within 48 hours of treatment. All cats underwent a thorough evaluation including physical examination, blood measurements and urinalysis (Table 1), blood pressure measurement, abdominal and thoracic radiography and abdominal ultrasonography. A cut-off value of >5.3 µg/L was used for Spec fPL concentration.[a] For 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylres-orufin) ester (DGGR)-lipase activity, the cut-off was set at >26 U/L based on the interval previously established in healthy cats (8-26 U/L).[16] For insulin-like growth factor 1 (IGF-1) a cut-off value of >1000 ng/mL was used in accordance to laboratory guidelines.[b] The experiment was approved by authorities in Switzerland (permission: 122/2011, 118/2014) and in Italy (permission: 16/79/2014, CE17/02/14). Informed consent was provided by owners.

Randomization and treatment

Enrolled cases were alternately assigned to 1 of 2 treatment groups. Both groups received insulin glargine[c] and a low-carbohydrate diet[d]. The initial insulin dosage was 1.0 IU, q12h, in cats weighing <4 kg and 1.5-2.0 IU, q12h, in cats ≥4 kg. One group received exenatide-ER[e] (200 µg/kg) and the other 0.33 mL of 0.9% saline solution (placebo); both treatments were

administered subcutaneously, once weekly. Owners were taught how to prepare and inject the exenatide-ER or placebo, but were unaware of the treatment group. If owners found this task problematic, a veterinarian administered the weekly injections.

Exenatide-ER was administered for 16 weeks or in cats that achieved diabetic remission, it was given for 4 weeks after discontinuing insulin therapy.

Follow-up

Successive follow-up evaluations were scheduled 1, 3, 6, 10 and 16 weeks after starting exenatide-ER or placebo. Each evaluation included assessment of clinical signs, physical examination, blood analysis (Table 1) and generation of a glucose curve. Owners were instructed to perform home-monitoring of blood glucose concentrations every 1-2 weeks starting 3 weeks after enrollment. To complete all curves, capillary blood glucose concentrations were measured every 2 hours for 8-12 hours using a validated portable blood glucose meter.[17] The insulin dosage was adjusted based on clinical signs and results of physical examination, glucose curves and serum fructosamine concentration; the goal was to resolve clinical signs of DM and to obtain curves with blood glucose ranging between 80-270 mg/dL and fructosamine concentrations between 350-450 µmol/L.[18] In cats that achieved remission, the insulin dose was decreased in increments of 0.5 IU per treatment, once weekly. The last dosage before insulin was discontinued was 0.5 UI once daily, for at least 1 week. The frequency, onset and duration of remission were recorded in both groups. The rate of metabolic control was evaluated at the end of the study. Criteria used to define remission and good metabolic control are explained in Table 2.

The frequency of hypoglycemia, defined as a blood glucose curve value ≤65 mg/dL, was determined. If owners observed clinical signs compatible with hypoglycemia (increased appetite,

restlessness, weakness, unsteady gait, loss of consciousness or cramps), they were instructed to measure capillary blood glucose concentration and to offer food or administer honey.

The median insulin dose per kg per day given during the study period was calculated for each cat. Two calculations were done; in one of them the phases of remission were excluded, in the other one the phases of remission were included.

Statistical analysis

Data are presented as median and ranges. Distribution of sex and breed, frequency of cases treated with antidiabetic medications before inclusion, and frequency of ketoacidosis recorded at admission were compared between cats receiving exenatide-ER and placebo using Fisher's exact test. The same test was used to compare the frequency of side effects and of hypoglycemic episodes, the rate and onset of remission and the rate of good metabolic control between groups. Differences between groups for age, body weight and laboratory results recorded at admission and for daily insulin dosage given over the 16-week study period were analyzed using the Mann-Whitney U-test. The same test was used to compare concentrations of fructosamine, Spec fPL, DGGR-lipase and creatinine concentrations between groups at each follow-up evaluation. Within each group, differences in body weight, body condition score (BCS)[f] and fructosamine, Spec fPL, DGGR-lipase and creatinine between baseline and the end of the study were investigated using the Wilcoxon signed rank test. A commercial software[g] was used. Significance was set at $P<0.05$.

Results

Animals

Of 52 cats with newly diagnosed DM admitted during the study period, 30 cats fulfilled the inclusion criteria and were enrolled. Each treatment group consisted of 15 cats. There were no significant differences between the two groups with regard to age, body weight, distribution of breeds or sex or frequency of cats previously treated with anti-diabetic medication (Table 3). On admission, 9 cats had ketoacidosis, which resolved within 1-2 days of treatment; 3 were allocated to the exenatide-ER group and 6 to placebo. The frequency of ketoacidosis did not differ between groups (P=0.427). None of the cats died during the study.

Side effects

Side effects recorded in cats treated with exenatide-ER and placebo are documented in Table 4. Most of the gastrointestinal side effects were self-limiting. In 1 cat that vomited 4 weeks after enrollment, the referring veterinarian prescribed cimetidine. Vomiting subsided, but recurred in week 10, at which time exenatide-ER treatment was discontinued. The frequency of side effects did not differ between groups (Table 4).

Skin lesions were not seen at the injection site of exenatide-ER or placebo. One cat treated with exenatide-ER developed non-pruritic histiocytic panniculitis, which was deemed unrelated to drug administration because it was 5-10 cm away from the injection site.

Hypoglycemia

Fourteen of 15 cats (93.3%) treated with exenatide-ER and 12 of 15 cats (80%) treated with placebo had episodes of biochemical hypoglycemia based on blood glucose curves; the frequency of hypoglycemic episodes did not differ between groups (P=0.598). Median glucose

concentration during hypoglycemia was 47 mg/dL (range: 25-65) in the exenatide-ER group and 50 mg/dL (range: 29-63) in the placebo group. Most of the cats did not have clinical signs of hypoglycemia. However, 2 cats with biochemical hypoglycemia in the exenatide-ER group had clinical signs compatible with hypoglycemia, including reduced appetite, vomiting and lethargy. Episodes of hypoglycemia were observed more often in weeks 6 and 7 in the exenatide-ER group and in weeks 8 to 12 in the placebo group (Figure 1).

Laboratory results and insulin dosage administered during the study

Baseline results of a complete blood count, biochemical profile, urinalysis and blood pressure measurement did not differ between groups (Table 5); positive urine culture was seen in 1 (6.7%) cat in the exenatide-ER group and in 2 (13.3%) in the placebo group.

In cats treated with exenatide-ER, the median fructosamine concentration was 620 µmol/L (range: 402-883) at baseline and 361 µmol/L (range: 267-483) after 16 weeks. In the placebo group, the median fructosamine concentration was 582 µmol/L (range: 438-878) at baseline and 377 µmol/L (range: 256-718) after 16 weeks. A significant decrease in serum fructosamine concentration was observed in both groups (P=0.001, each). Differences between groups were not identified at any time point.

In both groups, at the end of the study concentrations of Spec fPL [exenatide-ER: 1.8 µg/L (range: 0.6-25.4); placebo: 2.15 µg/L (range: 1.0-14.3); P=0.115, P=0.650, respectively] and DGGR-lipase [exenatide-ER: 19 U/L (range: 10-89); placebo: 18.5 U/L (range: 12-56); P=0.372, P=0.479, respectively] did not differ to baseline concentrations (Table 5). There was no difference in the concentration of either enzyme between groups at any time point (Figure 2). In the exenatide-ER group, baseline Spec fPL concentration was higher than normal in 3 (20%) cats and remained increased throughout the study. The Spec fPL was higher than normal at 16 weeks

in 1 of the 12 (8.3%) cats with a baseline Spec fPL concentration ≤5.3 µg/L. In the placebo group, the baseline Spec fPL concentration was higher than normal in 5 (33.3%) cats, and it remained increased throughout the study in 2 of them. Two of 10 (20%) cats with initial Spec fPL concentrations ≤5.3 µg/L had higher than normal Spec fPL concentrations after 16 weeks (Figure 2A). The concentration of serum DGGR-lipase was measured in 23 of the 30 cats. In the exenatide-ER group, baseline serum DGGR-lipase concentration was higher than normal in 4 of 11 (36.4%), and remained elevated throughout the study in 3 of them. In the placebo group, baseline serum DGGR-lipase concentration was higher than normal in 5 of 12 (41.7%) cats, and remained elevated throughout the study in 4 of them (Figure 2B). The concentration of serum DGGR-lipase did not increase by the end of the study in any of the cats that had normal baseline concentrations. Cats with increased Spec fPL or DGGR-lipase concentrations did not have obvious clinical signs or ultrasonographic evidence of pancreatitis.

In the exenatide ER group concentration of creatinine was slightly above the reference range in 1 (6.7%) cat at baseline but it normalized by the end of the study. Creatinine significantly increased from baseline (Table 5) to the end of the study in both groups [exenatide-ER: 1.4 mg/dL (range: 1.1-1.9); placebo: 1.4 mg/dL (range: 1.0-1.9); P=0.012, P=0.005, respectively], although in only 1 cat per group it slightly exceeded the reference range. Differences between groups were not identified at any time point.

The median concentration of IGF-1 was 372 ng/mL (range: 227-1163 ng/mL) in the exenatide-ER group and 405 ng/mL (range: 167-1041 ng/mL) in the placebo group. There was no significant difference between groups (P=0.408). One cat of each group had an IGF-1 concentration >1,000 ng/mL, but neither developed clinical signs of acromegaly, and both achieved remission at week 8 and 10, respectively. Computed tomographic examination of the head of 1 of the 2 cats revealed an unremarkable pituitary gland.

The median insulin dosage administered to cats receiving exenatide-ER or placebo during the study did not differ [exenatide-ER: 0.41 IU/kg/day (range: 0.11-0.88); placebo: 0.38 IU/kg/day (range: 0.22-1.5); *P*=0.663] (Figure 3). The median insulin dose administered during the study in cats also did not differ if phases of remission were not excluded from the calculation [exenatide-ER: 0.36 IU/kg/day (range: 0.07-0.88); placebo: 0.33 IU/kg/day (range: 0.13-1.5); *P*=0.494].

Body weight

In the exenatide-ER group, body weight decreased in 6 cats (40%) [median: -0.22 kg (range: -0.14 to -0.64)], increased in 8 (53.3%) [median: +0.89 kg (range: +0.20 to +1.50)] and did not change in 1 (6.7%) during the study period. In the placebo group, body weight decreased in 2 cats (13.3%) [median: -0.28 kg (range: -0.2 to -0.35)] and increased in 13 (86.7%) [median: +0.76 kg (range: +0.18 to +2.00)]. Overall, median body weight increased in both groups during the study; the increase was significant in the placebo group (*P*=0.002), but not in exenatide-ER treated cats (*P*=0.084) (Figure 4). BCS increased significantly in the placebo group (*P*=0.002), but not in the exenatide-ER group (*P*=0.058) (BCS are provided in Table 6).

Remission and metabolic control

Remission of DM was achieved in 6 (40%) cats treated with exenatide-ER and in 3 (20%) cats treated with placebo (*P*=0.427). All cats that achieved remission had no relapse of DM until the study end. In the exenatide-ER group, remission occurred 10-14 weeks (median: 11 weeks) after initiation of treatment, and in the placebo group, 8-10 weeks (median: 10) after initiation of treatment; the onset of remission did not differ between groups (Table 7). Good metabolic control was obtained in 8 of 9 (88.9%) non-remission cats in the exenatide-ER group, and in 7 of 12 (58.3%) non-remission cats in the placebo group (*P*=0.178). If cats in remission were grouped

together with those achieving good metabolic control, 14 of 15 (93.3%) diabetic cats treated with exenatide-ER had remission or good metabolic control compared with only 10 of 15 (66.7%) diabetic cats treated with placebo (P=0.169).

Discussion

In humans with type 2 DM, exenatide-ER administration is generally well tolerated, although transient and mild gastrointestinal side effects are frequently reported.[5,6,20] Gastrointestinal side effects of exenatide-ER have been described recently in healthy cats,[14] and were the most common side effect in the present study. They were usually mild and self-limiting which was an in agreement with findings in other species.[3] Although the etiology is not fully understood, reduced gastric emptying caused by GLP-1 analogues might be partially responsible.[2,21] Increased duration of sleeping and hiding in dark areas were frequently reported by owners of diabetic cats treated with exenatide-ER, but these behaviors were observed in the placebo group as well. Because side effects were not clearly associated with exenatide-ER in the present study and none was moderate to severe or long-lasting, we assume that the GLP-1 analogue can be safely used in diabetic cats. Of note, injection-site irritation as well as nodular, eosinophil-rich, granulomatous panniculitis at the injection site of exenatide have been described in humans.[22,23] To date, dermatologic irritation has not been reported in cats.[10,12,14] Skin nodules that were identified in 1 of our diabetic cats were likely unrelated to exenatide-ER injections. The lesions were non-pruritic, 5 to 10 cm from the injection site and diagnosed histologically as histiocytic panniculitis, all of which suggest that exenatide-ER was not the cause.

There have been concerns about incretin-based therapies and pancreatitis in humans, but studies did not find a significant association.[24,25] The Food and Drug Administration and the European Medicines Agency recently stated that it is currently unclear whether there is a causal relationship between incretin-based drugs and pancreatitis.[26] To our knowledge, a possible association between incretin-based therapy and pancreatitis in cats has not been investigated. Our previous research showed that many cats with DM may have subclinical pancreatitis.[27] In the present study, some cats treated with exenatide-ER had clinical signs that included reduced appetite and

vomiting; however, it is not known whether this was because of the drug, pancreatitis or some other cause. In the exenatide-ER group, only 1 (8.3%) cat with normal baseline Spec fPL and DGGR-lipase concentrations had an increase in Spec fPL concentration during treatment, possibly suggesting drug-induced pancreatitis. We cannot exclude the possibility that exenatide-ER increases the risk of pancreatic adverse effects in some diabetic cats, but further studies are required to clarify this.

An increase in creatinine concentration has been reported in some humans treated with GLP-1 analogues, which suggests that renal failure may occur or worsen during therapy. Based on this information, exenatide treatment is not recommended, particularly in patients with severe renal impairment.[h] In the present study, the increase in serum creatinine did not differ between the two groups. In most cats, creatinine concentrations stayed within the normal range. However, diabetic cats with relevant kidney disease were excluded; it is therefore possible that an increase in creatinine concentration would have occurred if diabetic cats with renal failure had been included. This finding might be explained by the fact that body weight, and possibly muscle mass along with creatinine, augmented in most cats during insulin treatment.

An investigation of type 2 diabetic humans receiving insulin glargine and short-acting exenatide or placebo showed that the incidence of hypoglycemic episodes was similar in both groups.[28] In healthy cats treated with exenatide-ER biochemical hypoglycemia was seen, whereas clinical hypoglycemia did not occur.[12] Similarly, in the present study biochemical hypoglycemia was a common finding, however there was no difference between the 2 groups. Clinical hypoglycemia was seen in 2 cats of the exenatide-ER group. As these were 2 single episodes which were short-lived, we hypothesize that exenatide-ER is safe when used in conjunction with insulin to treat diabetic cats.

Compared with the results of other studies of diabetic cats, the remission rates in the present investigation were relatively low in both groups. Other studies have followed diabetic cats for longer periods of time (e.g. 6 months) than our study (4 months),[29,30] and it is therefore possible that more cats would have achieved remission if the study had been longer. In addition, it is known that the rate of remission is higher if diabetic cats have received corticosteroids before diagnosis of DM.[18] In the present study cats with prior corticosteroid administration were not used, whereas in one other study with high remission rate those cats were included.[31] This difference in selection criteria may explain at least in part the different remission rates. Furthermore, our definition of remission was the maintenance of euglycemia without insulin treatment for 4 weeks, whereas an other study defined remission as 2 weeks of euglycemia without insulin.[31] If we had used this latter definition, there would have been 2 additional cats in remission in the exenatide-ER group, and thus the rate of remission would have increased from 40% to 53.3% (8 of 15 cats).

In humans with type 2 DM, exenatide-ER once weekly was superior to other GLP-1 analogues in controlling blood glucose concentrations.[5,6] Exenatide-ER, in addition to oral antidiabetic agents, was also able to provide better glycemic control than insulin detemir.[32] The present study shows that the percentage of cats that achieved good metabolic control was higher in the exenatide-ER group than the placebo group (93.3% vs. 66.7%, respectively) when cats in remission were grouped together with those with good metabolic control. The difference between groups was not significant because of the relatively low number of cats, but significance ($P<0.05$) would have been achieved if there had been 15 instead of 14 cats with good metabolic control or remission in the exenatide-ER group.

In humans with type 2 DM, treatment with GLP-1 analogues is associated with weight loss whereas insulin glargine therapy is associated with weight gain.[32] Weight loss was described in

healthy cats during treatment with exenatide or liraglutide.[11,13] In the present study, a significant weight gain and increase in BCS were seen in cats of the placebo group, likely due to the anabolic effect of insulin therapy; however, the increase was not significant in the exenatide-ER group. Prevention of weight gain is advised in diabetic cats with a high BCS, while weight gain to normalize body condition is preferable for diabetic cats with a low BCS. In general, exenatide-ER administration increased BCS in those with low baseline BCS, but did not increase BCS in cats with high baseline BCS. In humans treated with GLP-1 analogues, weight control can be attributed to a reduction in appetite because of increased satiation and a delay in gastric emptying.[20,33]

This study had some limitations including the relatively low number of cats; significant differences for rates of remission and good metabolic control may have been seen in a larger number of diabetic cats. Furthermore, the follow-up period was set at 4 months and it is possible that more cats would have achieved remission or good metabolic control if a longer study period had been chosen.

In summary, exenatide-ER is not associated with local or systemic side effects and can be safely used in diabetic cats. Exenatide-ER treatment does not result in a significant increase in body weight and may improve the rate of remission and metabolic control, although further studies using large cohorts are required.

Footnotes

[a]http://vetmed.tamu.edu/gilab/service/assays/pli

[b]NationWide, Specialist Laboratories, Cambridge, England

[c]Lantus, Sanofi Aventis, Meyrin, Switzerland

[d]DM Purina Veterinary Diets, Medical Solution, Steinhausen, Switzerland

[e]Bydureon, Amylin Pharmaceuticals, San Diego, CA

[f]Body condition chart (cat); Nestlé Purina, St. Louis, MO

[g]SPSS 18.0, SPSS, Chicago, IL

[h]http://www.fda.gov/safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm

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Tables

Table 1. Blood and urine examinations at baseline and during all follow-up examinations.

Blood analysis	**Baseline**	**Follow-up**
Complete blood cell count	+	+
Biochemical profile	+	+
Fructosamine	+	+
T4	+	
Spec fPL	+	+
IGF-1	+	
Urinalysis with UPC and culture	+	

UPC, urine protein-to-creatinine ratio

Table 2. Criteria used to define remission and good metabolic control in cats with DM.[15,18,19]

Endpoint	Clinical signs	Fructosamine (µmol/L)	Glucose (mg/dL)	Insulin treatment
Remission	absent	<350	72-162	No (for ≥4 weeks)
Good metabolic control	absent	350-450	80-270	Yes

Table 3. Signalment of diabetic cats and pretreatment with antidiabetic medications before inclusion in the study.

Animals	**Exenatide-ER (n=15)**	**Placebo (n=15)**	***P*-value**
Age, range and median in years	4.3-14.0 (9.3)	2.6-15.0 (10)	0.547
Body weight, range and median in kg	4.4-7.4 (5.3)	2.7-8.3 (4.5)	0.110
Domestic short- or longhair	12 (80%)	14 (93.3%)	0.598
Purebred	3 (20%)	1 (6.7%)	
Neutered male	9 (60%)	5 (33.3%)	
Intact male	1 (6.7%)	0 (0%)	0.143
Spayed female	5 (33.3%)	10 (66.7%)	
Pretreatment*	8 (53.3%)	10 (66.7%)	0.710

*antidiabetic medications received before inclusion.

Table 4. Type, time of occurrence and duration of side effects in diabetic cats treated with exenatide-ER or placebo.

	Exenatide-ER			Placebo			*P*-value
Side effect	**Cats (n=15)**	**Dpi***	**Between week**	**Cats (n=15)**	**Dpi***	**Between week**	
Reduced appetite	9 (60%)	1 to 3	1 to 10	3 (20%)	0 to 7	2 to 6	0.060
Vomiting	8 (53.3%)	1 to 4	0 to 15	6 (40%)	1 to 6	0 to 16	0.715
Diarrhea	1 (6.7%)	6	1 to 14	3 (20%)	1 to 3	1 to 14	0.598
Increased sleeping	5 (33.3%)	1-3	1 to 6	1 (6.7%)	1-3	0 to 6	0.169
Hiding in dark areas	3 (20%)	0 to 3	0 to 3	1 (6.7%)	1	9	0.598

* Dpi, days post injection.

Table 5. Laboratory results and blood pressure measurements at baseline in diabetic cats treated with exenatide-ER vs. placebo. Range and median values are given.

Parameter	**Exenatide-ER**	**Placebo**	**Reference interval**	***P*-value**
Hematocrit (%)	29-47 (37)	25-47 (34)	33-45	0.254
Leukocytes (10^3/µL)	3.2-20.5 (8.9)	4.8-22.1 (10.8)	4.6-12.8	0.165
Platelets (10^3/µL)	207-525 (340)	156-672 (347)	180-680	0.923
Glucose (mg/dL)	101-810 (392)	70-536 (428)	72-162	0.543
Fructosamine (µmol/L)	402-883 (620)	438-878 (582)	202-340	0.604
Cholesterol (mg/dL)	132-565 (256)	112-662 (267)	101-263	1.000
Triglycerides (mg/dL)	26-350 (79)	35-3478 (70)	26-114	0.537
Total protein (g/dL)	6.4-11.4 (7.4)	6.3-8.3 (7.4)	6.4-8.0	0.405
Albumin (g/dL)	3.1-4.1 (3.6)	2.7-4.4 (3.5)	3.0-4.0	0.884
Urea (mg/dL)	17.6-52.1 (30.0)	21.6-37.2 (29.1)	20.7-35.3	0.494
Creatinine (mg/dL)	0.9-1.9 (1.1)	0.6-1.7 (1.2)	1.1-1.8	0.527
Sodium (mEq/L)	145-165 (157)	145-165 (158)	158-165	0.967
Chloride (mEq/L)	99-126 (118)	105-121 (116)	121-131	0.220
Potassium (mEq/L)	4.3-5.4 (4.7)	3.4-5.9 (4.8)	3.8-5.4	0.755
Phosphorus (mg/dL)	2.7-6.5 (4.5)	2.5-5.0 (4.2)	2.8-5.6	0.130
Calcium (mg/dL)	1.1-11.9 (10.3)	9.3-11.9 (10.4)	9.6-11.2	0.967
Bilirubin (mg/dL)	0.02-0.43 (0.09)	0.01-0.43 (0.08)	0-0.2	0.747
ALP (U/L)	30-112 (50)	32-92 (49)	16-43	0.975
ALAT (U/L)	34-424 (76)	33-379 (87)	34-98	0.709
ASAT (U/L)	19-215 (29)	17-133 (41)	19-44	0.184
DGGR-Lipase (U/L)	11-92 (25)	13-48 (23)	8-26	0.734
Spec fPL (µg/L)	0.6-41.8 (2.2)	0.6-16.8 (3.0)	>5.3	0.878

T4 (µg/L)	0.7-2.4 (1.5)	0.5-1.8 (1.4)	<3.5	0.361
IGF-1 (ng/mL)	227-1163 (372)	167-1041 (405)	<1000	0.408
UPC	0.08-1.04 (0.22)	0.1-1.2 (0.2)	≤0.40	0.913
SAP (mm Hg)	96-224 (144)	85-189 (145)	80-160	0.573

ALP, alkaline phosphatase; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; UPC, urine protein-to-creatinine ratio; SAP, Systolic arterial pressure.

Table 6. Body condition score in diabetic cats treated with exenatide-ER or placebo at baseline (week 0) and at week 16. Within each group, cats are divided according to their body weight at week 16, which is compared to week 0 and reported as increased, decreased or no change.

			BCS (1-9)	
Group	**Body weight after 16 weeks**	**Number of cats**	**Week 0**	**Week 16**
Exenatide-ER	Increased	2	4	5
		1	4	6
		2	5	5
		2	5	6
		1	7	8
	Decreased	2	4	4
		2	5	5
		1	6	6
		1	6	5
	No change	1	5	5
Placebo	Increased	1	3	4
		1	3	5
		3	4	5
		3	5	6
		2	6	6
		1	6	8
		1	7	8
		1	7	9
	Decreased	2	5	5

Table 7. Onset of remission in diabetic cats treated with exenatide-ER or placebo (*P*=0.167).

Onset of remission	**Exenatide-ER (number of cats)**	**Placebo (number of cats)**
0-6 weeks after discharge	0	0
7-10 weeks after discharge	2	3
11-16 weeks after discharge	4	0

Figures

Figure 1. Number of diabetic cats with episodes of hypoglycemia during the 16-week study period.

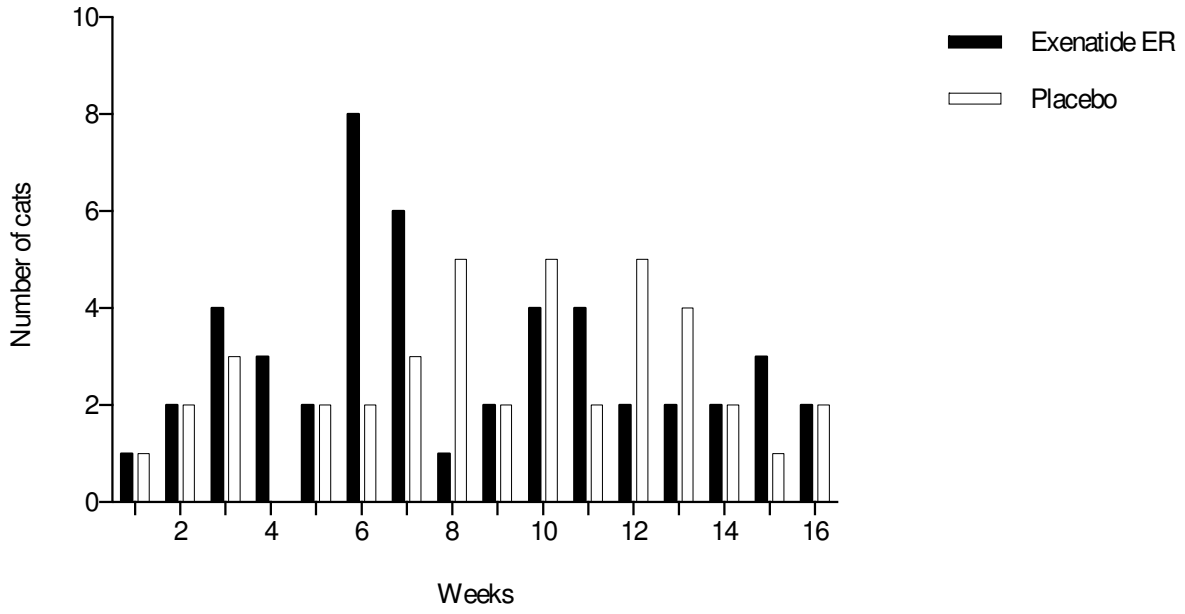


Figure 2. Serum concentration of Spec fPL (A) and DGGR-lipase (B) in exenatide-ER- and placebo-treated cats during the 16-week study period. Medians are shown. Dashed lines identify the reference interval. There were no differences between the groups.

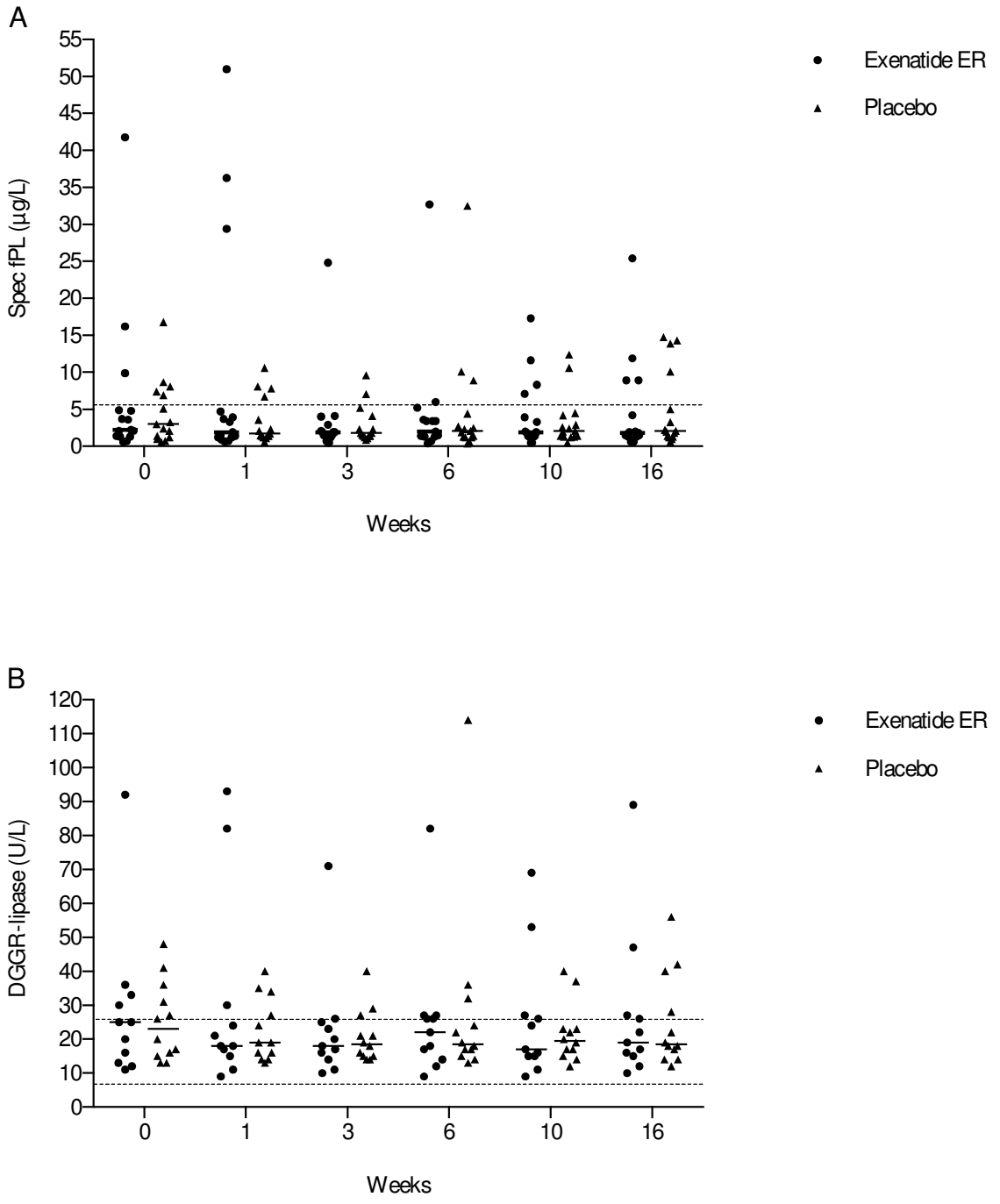


Figure 3. Dot plots of median insulin dose administered per kg body weight per day in cats receiving exenatide-ER or placebo. Horizontal lines mark the group medians.

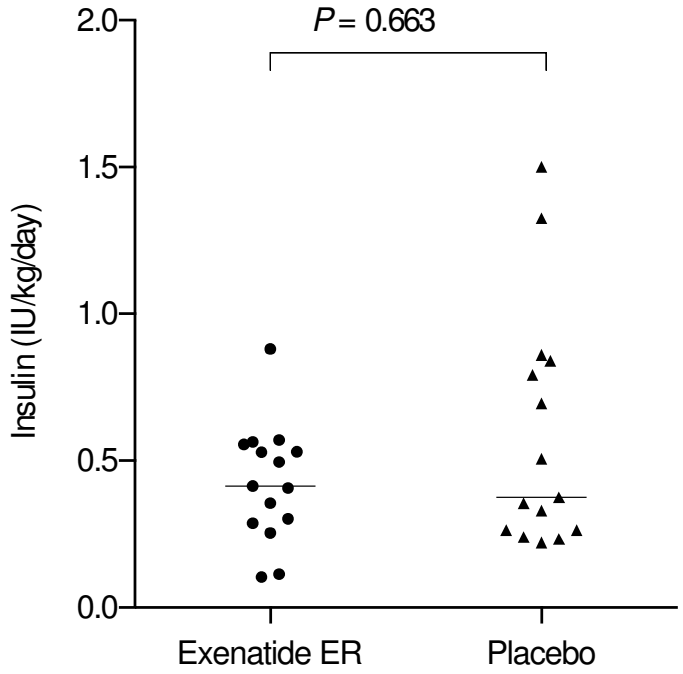
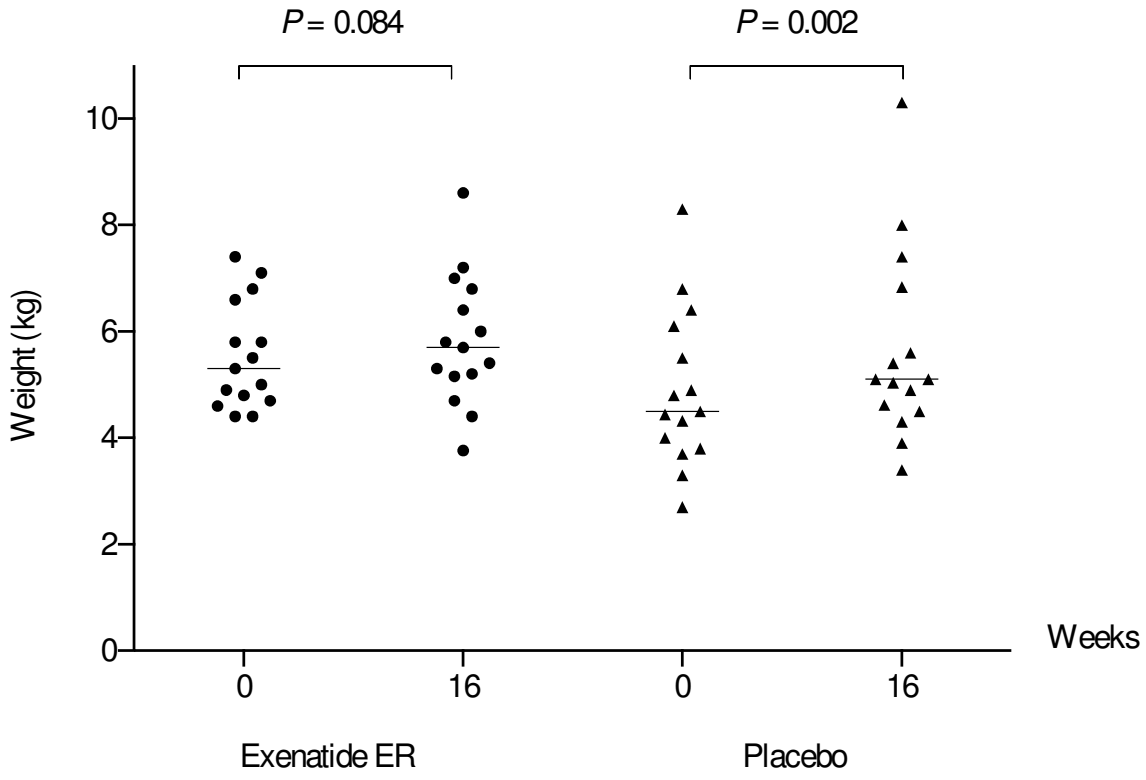


Figure 4. Body weight of cats of the exenatide-ER and placebo groups at baseline and week 16. Horizontal lines indicate the median body weight.



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