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Pharmacokinetics and pharmacodynamics of the glucagon-like peptide-1 analog liraglutide in healthy cats

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) is an intestinal hormone that induces glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion. Glucagon-like peptide-1 also increases beta cell mass and satiation while decelerating gastric emptying. Liraglutide is a fatty-acid derivative of GLP-1 with a protracted pharmacokinetic profile that is used in people for treatment of type II diabetes mellitus and obesity. The aim of this study was to determine the pharmacokinetics and pharmacodynamics of liraglutide in healthy cats. Hyperglycemic clamps were performed on days 0 (HGC) and 14 (LgHGC) in 7 healthy cats. Liraglutide was administered subcutaneously (0.6 mg/cat) once daily on days 8 through 14. Compared with the HGC (mean ± standard deviation; 455.5 ± 115.8 ng/L), insulin concentrations during LgHGC were increased (760.8 ± 350.7 ng/L; $P = 0.0022$), glucagon concentrations decreased (0.66 ± 0.4 pmol/L during HGC vs 0.5 ± 0.4 pmol/L during LgHGC; $P = 0.0089$), and there was a trend toward an increased total glucose infused (median [range] = 1.61 (1.11–2.54) g/kg and 2.25 (1.64–3.10) g/kg, respectively; $P = 0.087$). Appetite reduction and decreased body weight (9% ± 3%; $P = 0.006$) were observed in all cats. Liraglutide has similar effects and pharmacokinetics profile in cats to those reported in people. With a half-life of approximately 12 h, once daily dosing might be feasible; however, significant effects on appetite and weight loss may necessitate dosage or dosing frequency reductions. Further investigation of liraglutide in diabetic cats and overweight cats is warranted.

1. Introduction

Feline diabetes mellitus (FDM) closely resembles type 2 diabetes mellitus in people, as both FDM and type II diabetes mellitus (T2DM) are characterized by insulin resistance, relative insulin deficiency, decreased beta cell mass, and islet-amyloid depositions [1,2].

Despite technological advances in insulin formulations and monitoring, insulin therapy across species is still commonly associated with inadequate glycemic control leading to short- and long-term complications such as hypoglycemia, weight gain, and vascular diseases. Incretin-based therapy for T2DM was first introduced in 2005 and has quickly become a widely used adjunctive therapy. The incretin effect is the greater release of insulin occurring after oral glucose administration compared with intravenous administration of the same glucose dose. Two peptide hormones contribute to the incretin effect and are called incretin hormones: glucagon-like peptide-1 and glucose-dependent insulinotropic peptide (GIP). They are secreted from specialized enteroendocrine cells in response to the presence of nutrients in the lumen of the gut (but not in

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response to the presence of nutrients in the blood). By enhancing the response of pancreatic beta cells to glucose, GIP and GLP-1 enhance insulin secretion during hyperglycemia, thus leading to the incretin effect. In diabetics, the beta-cell response to GIP is diminished or absent. In contrast, GLP-1 retains its stimulatory effect in pancreatic beta-cells in diabetics, making it a more suitable candidate for diabetic therapy [3,4]. The American Diabetes Association recommends use of a glucagon-like peptide-1 receptor (GLP-1R) agonist as 1 of 5 additional therapeutic drugs to consider when lifestyle change and metformin therapy fail to achieve good glycemic control in patients with T2DM [5]. Beneficial effects of incretin therapy for T2DM in people include restoration of glucose sensitivity of pancreatic beta-cells, induction of glucose-dependent stimulation of insulin secretion while simultaneously suppressing glucagon secretion, inhibition of beta-cell apoptosis and increased beta-cell neogenesis, as well as slowing gastric emptying rate and enhancing satiation peripherally and centrally [3]. These effects result in decreased risk of treatment-associated hypoglycemia, improved beta-cell function, and weight loss [6–8]. Recently, nonglucose-dependent effects in cardiovascular health in people have been recognized, and research continues into the possible use of incretin therapy for neuropathic disorders [9]. The active forms of endogenous GLP-1 in humans include GLP-1(7–37) and GLP-1(7–36). Both forms are quickly degraded (within 1–2 min) in the body by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4) to inactive metabolites [3]. Liraglutide is a synthetic GLP-1R agonist which differs from endogenous GLP-1 by the substitution of lysine for arginine at position 34, and the attachment of a C-16 fatty acid (palmitoyl acid) at position 26. These changes in molecular structure allow liraglutide to bind to interstitial albumin and avoid metabolic degradation, lending the drug a half-life of 13 h in humans after subcutaneous injection [10].

The purpose of this study was to investigate the pharmacokinetics and pharmacodynamics of liraglutide therapy in healthy laboratory cats. We hypothesized that liraglutide would result in a glucose-dependent stimulation of insulin secretion, inhibition of glucagon secretion, and improved glucose tolerance.

2. Materials and methods

2.1. Animals

The study protocol was approved by The Ohio State University Institutional Animal Care and Use Committee. Eight healthy purpose-bred cats were used in this study, including 6 castrated males and 2 spayed females. All cats were 3 years old. In the beginning of the study, mean ± standard deviation (SD) (range) body weight was 5.5 ± 1.0 kg (4.7–7.0 kg). Five of the cats were overweight (body condition score was 5/9 in 3 cats, 6/9 in 2 cats, 7/9 in 1 cat, and 8/9 in 2 cats) [11]. Cats were group-housed in AAALAC accredited facilities. All cats were acclimatized and socialized for 4 wk before the start of experiments with environmental enrichment provided. Cats were fed ad lib a dry commercial cat food (IAMS Proactive Health Original with Chicken) by twice-daily timed-feedings. Appetite was assessed indirectly by observing the amount of food left in food bowls in individual cages during daily timed feedings. Daily physical examinations were performed, and body weight was monitored at least weekly. Body weight was stable in all cats during the acclimatization period. Routine laboratory tests (including complete blood counts, serum biochemistry, total thyroxine, coagulation profile, and urinalysis) were performed on days −1, 15, and 28 of the experiment.

2.2. Study design

A repeated-measures study design was used for the pharmacodynamics aspect of the study. Cats were maintained in a fasting state for 14 h before each clamp procedure. Hyperglycemic clamps (see the following) were performed on days 0 and 14. Subcutaneous injections of liraglutide (Victoza 18 mg/3 mL multi-dose pen, Novo Nordisk, Copenhagen, Denmark) were administered once daily with the use of a 32-gauge hypodermic needle that was attached to the prefilled injection pen, as directed by the manufacturer. The injection was administered in a previously shaved area on the cranial dorsum. The pen was set to deliver a fixed dose of 0.6 mg (mean dose 0.112 ± 0.019 mg/kg). Liraglutide was injected in each cat on days 1 and 8 through 14 of the study. The LgHGC was performed 2 h after the final liraglutide injection.

2.3. Hyperglycemic clamp procedure

Blood glucose (BG) concentrations were measured 90 min before each clamp procedure to ensure that stress-related hyperglycemia was not present. Blood glucose was measured at −15 and 0 min and averaged to obtain baseline fasting BG concentrations. Beginning at time zero, blood glucose was measured every 5 min for 90 min with a hand-held point-of-care glucose meter (AlphaTRAK 2; Abbott Animal Health, Abbott Park, IL) [12]. Also beginning at time zero and for the next 90 min, 20% dextrose (an in-saline dilution of 50% Dextrose USP; VETONE, MWI, Boise, ID) was infused intravenously (through a cephalic catheter) at a changing rate. In the first 30 min (adjustment period), dextrose was administered at an increasing rate to achieve hyperglycemia at a target of 225 mg/dL (range 200–250 mg/dL). The infusion rate was determined based on the 5-min BG measurements. In the final 60 min of the procedure (hyperglycemic-clamp period), the dextrose infusion was adjusted as necessary to maintain target BG. Samples were collected for measurement of insulin and glucagon concentrations at baseline (−15 and 0 min) and 30, 45, 60, 75, and 90 min. Blood samples for glucose and hormones measurements were collected via jugular catheters.

2.4. GLP-1 pharmacokinetics study

The pharmacokinetics of liraglutide was evaluated after a single subcutaneous injection on day 1. Cats were maintained in a fasting state for 14 h before the injection. Blood samples for measuring liraglutide concentrations were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 84 h.