Domestic Animal Endocrinology 51 (2015) 78–85

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.domesticanimalendo.com

Pharmacology of the glucagon-like peptide-1 analog exenatide extended-release in healthy cats

A.J. Rudinsky [a], C.A. Adin [a], S. Borin-Crivellenti [b], P. Rajala-Schultz [c], M.J. Hall [a], C. Gilor [a,*]

[a] Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210, USA
[b] FAPESP (#2013/00027-6) and FCAV, Universidade Estadual Paulista (UNESP), Jaboticabal, Sao Paulo, Brazil
[c] Department of Veterinary Preventive Medicine, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210, USA

ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form 8 December 2014
Accepted 11 December 2014

Keywords:
Feline
Exenatide
Incretin
Diabetes
Insulin
Glucagon

ABSTRACT

Exenatide extended-release (ER) is a microencapsulated formulation of the glucagon-like peptide 1-receptor agonist exenatide. It has a protracted pharmacokinetic profile that allows a once-weekly injection with comparable efficacy to insulin with an improved safety profile in type II diabetic people. Here, we studied the pharmacology of exenatide ER in 6 healthy cats. A single subcutaneous injection of exenatide ER (0.13 mg/kg) was administered on day 0. Exenatide concentrations were measured for 12 wk. A hyperglycemic clamp (target = 225 mg/dL) was performed on days −7 (clamp I) and 21 (clamp II) with measurements of insulin and glucagon concentrations. Glucose tolerance was defined as the amount of glucose required to maintain hyperglycemia during the clamp. Continuous glucose monitoring was performed on weeks 0, 2, and 6 after injection. Plasma concentrations of exenatide peaked at 1 h and 4 wk after injection. Comparing clamp I with clamp II, fasting blood glucose decreased (mean ± standard deviation = −11 ± 8 mg/dL, $P = 0.02$), glucose tolerance improved (median [range] +33% [4%–138%], $P = 0.04$), insulin concentrations increased (+36.5% [−9.9% to 274.1%], $P = 0.02$), and glucagon concentrations decreased (−4.7% [0%–12.1%], $P = 0.005$). Compared with preinjection values on continuous glucose monitoring, glucose concentrations decreased and the frequency of readings <50 mg/dL increased at 2 and 6 wk after injection of exenatide ER. This did not correspond to clinical hypoglycemia. No other side effects were observed throughout the study. Exenatide ER was safe and effective in improving glucose tolerance 3 wk after a single injection. Further evaluation is needed to determine its safety, efficacy, and duration of action in diabetic cats.

1. Introduction

Diabetes mellitus (DM) remains one of the most common and clinically important diseases in feline medicine. Recent data show that the prevalence of both DM and obesity is increasing in recent years within the domestic feline population [1]. Various therapies have been used to manage the disease clinically including exogenous insulin administration subcutaneously, dietary modification, weight control, and management of insulin-resistant states. However, the vast majority of animals rely on daily insulin therapy to manage the disease, which is associated with various side effects, some of which can be life threatening [1].

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin

* Corresponding author. Tel.: +1 6149409831; fax: 1-614-292-0895.
E-mail address: gilor.1@osu.edu (C. Gilor).

0739-7240/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.domaniend.2014.12.003

hormones. They are secreted from the gastrointestinal tract into the circulation in response to ingestion of nutrients, and they enhance glucose-stimulated insulin secretion. These hormones are responsible for the incretin effect in which oral glucose administration is associated with a much greater increase in plasma insulin concentrations compared with intravenous glucose resulting in the same time course of plasma glucose levels. In human diabetics, the secretion of GIP is normal or slightly reduced, but its insulinotropic effects on the pancreas are markedly impaired. In contrast, GLP-1 retains its insulinotropic effects in type II diabetes, but secretion of GLP-1 is decreased. More importantly, the effects of incretin hormones are far more diversified than potentiation of insulin alone, including decreased glucagon secretion, induce satiation, and slowing gastric emptying [2].

As a result of the numerous beneficial effects in the diabetic state, incretin-based drugs have been developed and are commercially available for adjunctive treatment of type II DM in people [3–8]. Exenatide has been shown to be as effective as insulin glargine in the treatment of human type II DM but with fewer side effects such as weight gain and hypoglycemia [3]. In a 2-yr follow-up of human patients receiving exenatide, patients achieved sustained and significant reductions in glycosylated hemoglobin, accompanied by significant weight loss. However, most importantly, treatment with exenatide improved pancreatic beta-cell function and survival [5]. This has led to multiple GLP-1 analogs approved for use in the human medical field. Specifically, Bydureon (extended-release [ER] exenatide) has emerged as a therapeutic option with the same benefits as other GLP-1 analogs with a markedly reduced dosing frequency [9]. In studies comparing the efficacy of exenatide ER with short-acting exenatide, exenatide ER was associated with better glycemic control and reduced side effects because of a better correlation to physiological needs, less difficulty in achieving glycemic control, improved compliance, and most importantly, reduced risk of hypoglycemia [10–12].

The goal of exenatide ER is to provide sustained release of the drug with a once-weekly dosing regimen based on human pharmacokinetic studies [13,14]. This is accomplished through microsphere technology in which exenatide is incorporated into a biodegradable matrix for slow release in the subcutaneous compartment [9]. In humans, an initial peak is seen shortly after injection followed by a longer sustained period of action thereafter [13,14].

We hypothesized that exenatide ER administered subcutaneously would result in significant potentiation of insulin, suppression of glucagon secretion, and lower fasted blood glucose (BG) without the deleterious effects associated with exogenous insulin administration.

2. Materials and methods

2.1. Animals

All animal use was approved by The Ohio State University Institutional Animal Care and Use Committee. Six young, healthy, castrated male, purpose-bred cats were used in this study. All cats were 3-yr-old. Median body weight was 5.3 kg (range, 4.6–6.6 kg). Body condition score was 5 of 9 in 3 cats, 6 of 9 in 2 cats, and 7 of 9 in 1 cat [15,16]. Three of the cats were classified as overweight. Cats were group housed in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All cats were acclimatized and socialized for at least 8 wk before the start of experiments with environmental enrichment provided. Cats were fed a commercial cat food (IAMS Proactive Health Original with Chicken) by twice daily–timed feedings. Daily physical examinations were performed, and body weight was monitored weekly. Body weight was stable in all cats during the acclimatization period. Routine laboratory tests including complete blood counts, serum chemistry, coagulation profile, and urinalysis were performed at the beginning of the acclimatization period, at the onset of the experiment, and at the conclusion of the experiment.

2.2. Study design

2.2.1. Pharmacodynamics study

A repeated-measures study design was used: a hyperglycemic clamp (HGC) as described previously (see the following) was performed before (HGC, day −7) and after (ExHGC, day 21) a single subcutaneous injection (day 1) of exenatide ER (Bydureon Injectable Suspension, 0.13 mg/kg; Amylin Pharmaceuticals, Inc San Diego, CA, USA) [17]. During the HGC, BG concentrations were measured every 5 min, and dextrose was infused intravenously at a variable rate (depending on the previously measured BG) to achieve a target BG of 225 mg/dL. For dextrose intravenous infusion, a 50% dextrose solution (50% Dextrose USP; VetOne, MWI, Boise, ID, USA) was diluted with saline to a 20% solution. Infusion rate was set on a syringe pump. BG concentrations between 90 and 120 min before the HGC were obtained to monitor for marked hyperglycemia or hypoglycemia, in which case, the HGC would have been delayed. Ten minutes before the HGC, baseline BG concentrations were measured. BG concentrations were measured again at time 0, and then, every 5 min for a total of 90 min. The first 30 min of the HGC was used to obtain reliable BG concentrations of approximately 225 mg/dL, whereas the remaining 60 min was considered to be the HGC in which all statistical analyses were performed on blood samples. Blood samples for determining insulin and glucagon concentrations were collected at −15, 0, 30, 45, 60, 75, and 90 min. Cats were maintained in a fasting state for at least 14 h before each experiment.

2.2.2. Pharmacokinetics study and side effects

As described previously, on day 1, 0.13 mg/kg of exenatide ER was administered subcutaneously with the use of a 22-gauge hypodermic needle after reconstitution as directed by the manufacturer. The injection was administered in a previously shaved and marked area on the cranial dorsum. Blood samples for exenatide concentrations were collected immediately before injection (time 0) and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, and 48 h after and then once weekly until 12 wk. During each weekly blood sampling, collection of blood was performed at 7 AM just before the daily morning meal. In all cats, monitoring for potential