Domestic Animal Endocrinology 64 (2018) 17–30

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.journals.elsevier.com/domestic-animal-endocrinology

Pharmacodynamics and pharmacokinetics of insulin detemir and insulin glargine 300 U/mL in healthy dogs

H. Fink, C. Herbert, C. Gilor*,†

Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, 601 Vernon L Tharp St, Columbus, OH 43210, USA

ARTICLE INFO

Article history:
Received 21 June 2017
Received in revised form 30 March 2018
Accepted 30 March 2018

Keywords:
Diabetes mellitus
Isoglycemic clamp

ABSTRACT

Insulin glargine 300 U/mL and insulin detemir are synthetic long-acting insulin analogs associated with minimal day-to-day variability or episodes of hypoglycemia in people. Here, 8 healthy purpose-bred dogs each received 2.4 nmol/kg subcutaneous injections of insulin detemir (0.1 U/kg) and insulin glargine 300 U/mL (0.4 U/kg) on 2 different days, >1 wk apart, in random order. Blood glucose (BG) was measured every 5 min, and glucose was administered intravenously at a variable rate with the goal of maintaining BG within 10% of baseline BG ("isoglycemic clamp"). Endogenous and exogenous insulin were measured for up to 24 h after insulin injection. The effect of exogenous insulin was defined by glucose infusion rate or a decline in endogenous insulin. Isoglycemic clamps were generated in all 8 dogs after detemir but only in 4 dogs after glargine. Median time to onset of action was delayed with glargine compared to detemir (4.0 h [3.3–5.8 h] vs 0.6 h [0.6–1.2 h], $P = 0.002$). There was no difference in time to peak (median [range] = 6.3 h [5.0–21.3 h] vs 4.3 h [2.9–7.4 h], $P = 0.15$) or duration of action (16.3 h [6.1–20.1 h] vs 10.8 h [8.8–14.8 h], $P = 0.21$) between glargine and detemir, respectively. Glargine demonstrated a peakless time-action profile in 4/8 dogs. The total metabolic effect and peak action of detemir was significantly greater than glargine. Significant concentrations of glargine were detected in all but 1 dog following administration. Glargine might be better suited than detemir as a once-daily insulin formulation in some dogs based on its long duration of action and peakless time-action profile. Day-to-day variability in insulin action should be further assessed for both formulations.

1. Introduction

Insulin glargine 300 U/mL (Toujeo, Sanofi-Aventis, Bridgewater, NJ) and insulin detemir (Levemir, Novo Nordisk, Plainsboro, NJ) are synthetic long-acting insulin analogs. In human patients with type 1 and type 2 diabetes mellitus, insulin glargine 300 U/mL provides superior glycemic control to that of glargine 100 U/mL (Lantus), with less frequency of hypoglycemia and weight gain [1–7]. The more predictable pharmacodynamics (PD) of insulin glargine 300 U/mL and insulin detemir, demonstrated in human clinical trials, are key to minimizing hypoglycemic events [1–13]. Minimal data are available on the PD of insulin detemir in dogs and none on insulin glargine 300 U/mL [14–16].

Insulin glargine is human recombinant synthetic insulin in which asparagine at position A21 is replaced with glycine and 2 arginine residues are added to the C-terminus of the B chain at position B30. This synthetic molecule is completely water soluble at a pH of 4, but at physiologic pH (in the subcutaneous tissues) forms microprecipitates.

This article was presented in an abstract form at ACVIM 2017.

* Corresponding author. Tel.: +1 530 752 1363; fax: +1 530 752 0414.
E-mail address: cgilor@ucdavis.edu (C. Gilor).
† Present address: Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, Davis, CA 95616, USA.

0739-7240/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.domaniend.2018.03.007

These microprecipitates allow for slow and relatively predictable release from the tissues. Insulin glargine was first used in a concentration of 100 U/mL (Lantus). This formulation is widely used in people, and there are scant data on its use in dogs [14,17–20]. Recently, insulin glargine 300 U/mL has been evaluated in people and was found to have more predictable pharmacokinetics (PK) and PD profiles than that of glargine 100 U/mL. The metabolically active insulin is identical in Lantus and Toujeo; however, steady state PK profiles are significantly flatter and more prolonged for insulin glargine 300 U/mL compared to insulin glargine 100 U/mL. The higher concentration in insulin glargine 300 U/mL enables a more gradual and prolonged release from the subcutaneous (SQ) tissues following injection, resulting in an extended terminal half-life of 17 to 19 h in people. Compared to insulin glargine 100 U/mL, insulin glargine 300 U/mL has lower within-day and day-to-day variability in people, which increases its safety [1–7]. The time action profile of insulin glargine 300 U/mL has not yet been evaluated in dogs.

Insulin detemir is also human recombinant synthetic insulin. It differs from human insulin in that threonine at position B30 is replaced with a myristic acid residue (14-carbon fatty acid). Prolonged absorption from SQ tissues following injection results from hydrophobic interactions between fatty acids [17]. Reversible binding of albumin to the fatty acid residue allows buffering of insulin detemir in the blood and tissues, which contributes to its predictable effect. In people, insulin detemir provides more predictable glycemic control among patients and less within-day variability in individual patients compared to insulin glargine 100 U/mL [9–12]. The PD profile of insulin detemir has been evaluated in dogs, but only in 3 dogs, and only at doses that are likely too high to be clinically relevant (0.5 U/kg) [15].

In veterinary medicine, blood glucose (BG) curves have been used traditionally to evaluate the PD of exogenous insulin. Glucose curves, however, reflect not only the effect of exogenous insulin but also the effect of endogenous insulin and stress hormones. The isoglycemic clamp is considered the most suitable method for the study of PD of insulin in people because it enables the assessment of exogenous insulin without interference of endogenous hormones [21,22]. The goal of our study was to compare the PK and PD of insulin detemir and insulin glargine 300 U/mL (Toujeo) in healthy dogs. We hypothesized that after SQ administration of an equivalent molar dose, insulin glargine 300 U/mL (Toujeo) would have longer duration of action (DA) and flatter time-action profile compared with insulin detemir (Levemir), potentially making it more suitable for use as a once-daily injection in diabetic dogs.

2. Materials and methods

2.1. Animals

All animal use was approved by The Ohio State University Institutional Animal Care and Use Committee (Protocol number 2015A00000063). Two castrated Beagle males and 6 spayed mixed hound female dogs were used in this study. Median age was 2 yr (range 1–3 yr). Median body condition score (assessed by a single investigator [C.G.]) was 5 of 9 (range 4–7 of 9). Median body weight was 27 kg (range 10–30 kg). Dogs were housed individually in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All dogs were fed the same commercial dry dog food (Laboratory Canine Diet, CAT#5006, LabDiet, St. Louis, MO) as recommended by the manufacturer (to maintain body weight), twice daily at 8:00 AM and 4:30 PM. Dogs were deemed healthy based on the absence of clinical signs of disease, routine physical exams and a complete blood count, chemistry panel, and urinalysis.

2.2. Vascular access port and peripheral catheter placement and maintenance

In each dog, a vascular access port (VAPs; CompanionPort, CP 202K, Norfolk Vet Products, Skokie, IL) was surgically placed under general anesthesia at least 1 wk before beginning the experiment. The vascular access ports were maintained by a weekly 3 mL (500 U/mL) heparin lock injection. On the morning of each experiment, a peripheral intravenous catheter (20 gauge) was placed in a cephalic vein at least 1 h before the start of the experiment and removed at the end of it.

2.3. Pharmacodynamics study

Each dog received 2 SQ injections of insulin: 2.4 nmol/kg of insulin detemir [a] (0.1 U/kg) and 2.4 nmol/kg of insulin glargine [b] 300 U/mL (0.4 U/kg), on 2 different days, at least 1 wk apart (but no more than 4 wk apart) in random order (based on a coin flip). The dose was rounded up to the nearest 1 unit. Insulin was injected by a single investigator (C.G.) on the dorsum, midway between the scapulae. Experiments always began between 8:00 and 10:00 AM on a given day. Dogs were fasted overnight for 15 to 17 h before each experiment and remained fasted during the experiment.

All blood samples were collected through the vascular access ports. Cephalic catheters (Surflo, I.V. Catheter, 20G X 1", Terumo Medical Products, Somerset, NJ) were used exclusively for glucose (dextrose) infusion. For glucose infusion, a 50% dextrose solution (50% Dextrose USP; VET ONE, MWI, Boise, ID) was diluted with saline to a 20% solution. Infusion rate was set on a syringe pump (Medfusion 3500 syringe infusion pump 4.0 software). Blood glucose concentrations were measured with a hand-held point-of-care glucometer that was previously validated for use in dogs (Alphatrak 2, Zoetis Animal Health, range 20–750 mg/dL, intra-assay CV 3.8%).

After insulin injection, BG was maintained ("clamped") at a target isoglycemic concentration for the duration of the experiment by infusing glucose at a changing rate. Blood glucose concentrations were measured at −25, −15, time zero, and every 5 min thereafter, and the glucose infusion rate (GIR)

[a] Levemir: www.accessdata.fda.gov/drugsatfda_docs/label/2012/021536s037lbl.pdf.
[b] Toujeo: www.accessdata.fda.gov/drugsatfda_docs/label/2015/206538lbl.pdf.