WHAT'S NEW IN CANINE AND FELINE DIABETES MELLITUS

Chen Gilor DVM, PhD, DACVIM
University of California, Davis

INTRODUCTION

Insulin glargine 300U/ml (Toujeo®) and insulin degludec (Tresiba®) are synthetic insulin analogs that are used in people as basal insulin. In people, Toujeo® is more predictable and longer-acting compared to glargine 100U/ml (Lantus®) and Tresiba® is an ultra-long acting with a duration of action of over 40h that allows a flexible daily schedule of administration. In dogs and cats, very little is known about these formulations. Tresiba® has been studied in a small number of healthy cats and seem to have a much shorter duration of action in cats (about 11 hours) compared to people. Toujeo® has longer duration of action in cats (about 16 hours) and a relatively flat time-action profile. Toujeo® has been compared to insulin detemir in a small number of purpose-bred healthy dogs and seem to have lower potency (on a molar basis), longer duration of action, and a flat-time action profile. Overall, for use as a once daily injection, Toujeo® seems the best candidate out of currently available insulin formulation in both dogs and cats. The needed alterations in standard protocol that result from the use of a basal insulin are discussed below. Also discussed below is the physiologic and pharmacological background for use of the GLP-1 analog exenatide-ER, as well as current experience with this drug in cats. Exenatide-ER is revolutionizing human diabetes by allowing once-weekly treatments to replace daily insulin injections with greater efficacy and lower frequency of side effects.

INSULIN FORMULATIONS: GENERAL PRINCIPLES

Between-day variation in insulin action is a critical factor contributing to decreased glycemic control and risk of hypoglycemia. Factors that increase between-day variation include imprecision of dosing, variation in injection technique, and variation in rate of insulin absorption from the SQ depot. Dosing imprecision can be minimized by using insulin injection pens. Variation in absorption from the SQ depot is a significant contributor to between-day variation in insulin suspensions. In these traditional formulations (NPH, Lente, PZI), de-precipitation in the SQ depot is relatively erratic and results in relatively unpredictable time-action profile.[1] Novel formulations (detemir, degludec, glargine) are supplied as solutions and not suspension which increases dosing accuracy. Insulin detemir and insulin degludec also don't precipitate in the SQ depot and their absorption is much more predictable.[2,3]

With most traditional formulations (including NPH, Lente, PZI), a peak insulin action occurs after injection and that peak should coincide with post-prandial glucose absorption. Post-peak levels should meet the basal insulin requirements (fasting requirements) but should not exceed them.[2] However, achieving complete congruity between exogenous insulin action and endogenous insulin requirements during these 2 different phases is challenging at best, even if assuming complete consistency between meals, post-meal activity levels, stress, etc. Thus, to avoid hypoglycemia with a practical twice-daily insulin therapy and relatively infrequent monitoring, there has to be a tradeoff. In veterinary medicine this tradeoff is typically loose glycemic control with blood glucose concentrations ranging between 100 – 300 mg/dL with residual glycosuria and incomplete reduction of clinical signs. In people, because of the critical importance of tight glycemic control, the tradeoff is often a combination of more intensive blood glucose monitoring with a more intensive treatment protocol that combines bolus (ultra-short acting) formulations with basal (long-acting) formulations.[4]

NOVEL INSULIN FORMULATION IN HUMAN MEDICINE

Insulin glargine: Recombinant human insulin analog (Asparagine at A21 is replaced by glycine and 2 arginines are added at B31 and B32). This synthetic molecule does not tent to hexamerize at a pH of 4.0 but strongly crystalizes at pH = 7.2. Considered in people long-acting and "peakless".[2]

Three formulations of glargine are currently available on the market: Lantus® and Basaglar® are U100 formulation with similar pharmacological properties. Toujeo® is a U300 glargine formulation. Compared to Lantus®, Toujeo® has longer duration of action, decreased within-day variation and decreased between-day variation. Compared to glargine U100, Toujeo® is associated with decreased frequency of hypoglycemic events in diabetic people.[5]

Insulin detemir: Recombinant human insulin analog (B30 replaced by myristic acid – a 14-carbon fatty acid). Considered in people long-acting but not "peakless" and still as effective as insulin glargine as basal insulin (fewer side effects because more predictable). The fatty acid bound to insulin Levemir prevents formation of regular hexamers and allows hydrophobic interactions between detemir molecules and with albumin. These interactions allow more predictable absorption from the SQ depot and buffering of detemir concentrations by albumin which

leads to minimal variability in time-action profile from one day to the next and a better safety profile (minimal frequency of hypoglycemic events). Insulin detemir has other advantages that are likely related to its tendency to bind to albumin. After adjusting for its high potency and comparing at equivalent units of action in terms of glucose lowering effects, insulin detemir decreases endogenous glucose output and NEFA more than other insulin formulations.[6,7] This means that SQ administration of insulin detemir resembles the physiological effect of insulin more than other insulin formulations do. Insulin secreted from the pancreas and into the portal system reaches the liver in high concentrations. It is then degraded by the liver and eventually reaches peripheral target tissues in much lower concentrations (about 3 fold difference in dogs) so that overall endogenous insulin has more effect on shutting down endogenous glucose production than on peripheral glucose uptake.[7] By mimicking this differential effect insulin detemir causes less weight gain while maintaining the same degree of glycemic control.[2]

Insulin degludec: Recombinant human insulin analog in which B30 is replaced by a fatty acid (hexadecandioic acid) that is bound to B29 via a glutamic spacer. These changes allow for multi-hexamers to form in subcutaneous tissues and a long acting (half-life of apprx. 24h) and completely peakless time-action profile. Originally studied as an every-other-day formulation in people, it is now used as a once-daily injection with flexible time of injection. After a few days of daily administration, insulin degludec reaches steady state, with minimal inter-day fluctuation even when the time of injection is not constant.[3] This makes it an ideal basal insulin with greater patient compliance.

NOVEL INSULIN FORMULATION IN DOGS AND CATS

Dogs: Toujeo® was compared to insulin detemir (Levemir®) in 8 dogs and was found to have longer duration of action (approximately 16h vs. 11h respectively), and a relatively peakless time-action profile.[8] These properties make Toujeo® a more likely candidate as a basal once-daily insulin injection in dogs. Toujeo® also a much lower glucose-lowering effect compared to Levemir®, both when considered on a molar basis and on a unit basis. This makes. At a dose of 0.4U/kg, 4 out of 8 dogs did not need a glucose infusion to maintain their blood glucose normal, although endogenous insulin was suppressed in these dogs for over 16 hours. In comparison, an identical molar dose of Levemir® (0.1U/kg) necessitated glucose infusion to maintain euglycemia in all 8 dogs. In the 4 dogs that needed a glucose infusion after both insulin injections, the glucose lowering effect of Levemir® was 3 fold higher (range 1.1-6) compared to Toujeo®. This very low potency of Toujeo® might be an advantage in small dogs, allowing small alterations in effective dose with every unit change.

Cats: Insulin detemir (Levemir®) has similar potency, duration of action and over-all time action profile similar to that of Lantus®. In one study, the between-cat variability was lower for most pharmacodynamic parameters when comparing Levemir® to Lantus®. Recently, we compared insulin degludec (Tresiba®) to insulin glargine U300 (Toujeo®). Tresiba had a surprisingly short duration of action in cats (about 11h) although with very low inter-subject variability. Toujeo® was longer in duration (about 15h) with a relatively peakless time-action profile. Compared to historical data on Levemir® and Lantus®, Toujeo® is longer acting and with had lower inter-subject variation, making it most suitable as a basal once-daily insulin formulation.

GLP-1 ANALOGS

Incretin-based therapies are revolutionizing the field of diabetes therapy by replacing insulin therapy with safer and more convenient, long-acting drugs. Incretin hormones (GLP-1 and GIP) are secreted from the intestinal tract in response to the presence of food in the intestinal lumen. GLP-1 augments insulin secretion and suppresses glucagon secretion during hyperglycemia in a glucose-dependent manner. Clinical data have revealed that incretin-based drugs are as effective as insulin in improving glycemic control while reducing body weight (GLP-1 analogs, specifically) in patients with type 2 diabetes. Furthermore, incidence of hypoglycemia is relatively low with these drugs because of their glucose-dependent mechanism of action. Another significant advantage of these drugs is their duration of action. While insulin injections are administered at least once daily, long-acting GLP-1 analogs have been developed as once-a-week injections and could potentially be administered even less frequently than that in diabetic cats.

Exenatide: The peptide exendin-4 was first isolated from the poisonous venom of the Gila Monster (*Heloderma suspectum*). Exendin-4 is a 39-amino acid peptide that shares only a 53% sequence homology with GLP-1 but its affinity for the GLP-1 receptor is 1000 times greater than the affinity of GLP-1. Unlike GLP-1, exendin-4 is not a substrate for DPP-4 and NEP.[9] Exenatide is a synthetic exendin-4. Resistant to degradation, exenatide is eliminated by the kidneys and has a half-life of 3-4 hours in people. Its biological effect lasts about 8 hours after subcutaneous injection and it can be detected in the plasma for up to 15 hours.[10] Multiple studies, both *in vitro* and *in vivo*, have shown that, in general, exendin-4 has the same physiologic effects as GLP-1 in the pancreas, GI tract, and brain.[11] Exenatide is associated with improvement in some of the earliest and most fundamental abnormalities of type 2 diabetes: diminished “first-phase insulin response” and proinsulin/insulin ratio. Acute administration of exenatide in

type 2 diabetic patients corrects the abnormal insulin secretion pattern after an IV glucose bolus (first phase and second phase insulin responses) and restores the ability of beta cells to respond to rapid changes in blood glucose concentrations.[11] Exenatide also improves proinsulin/insulin ratio after 30 weeks of treatment.[12]

Exenatide has been shown to be as effective as insulin glargine in the treatment of DM but with less side effects (e.g. hypoglycemia and weight gain).[13] In a 2-year follow-up of patients receiving exenatide, patients achieved sustained and significant reductions in glycosylated hemoglobin, accompanied by significant weight loss (instead of weight gain commonly seen in diabetics receiving insulin) and improvement in serum liver enzyme activity and blood pressure. Most importantly, treatment with exenatide improved beta cell function as measured by homeostasis model assessment of beta cell function (HOMA-B).[14]

Exenatide has minimal side effects in people. It is mostly associated with nausea and less frequently with vomiting. Infrequently, it might cause hypoglycemia. Severe hypoglycemia (requiring assistance) was reported rarely (only 5 of 2781 patients) and only in patients who also received sulfonylurea drugs. Antibodies to exenatide developed in 67% of patients but this did not affect outcome and was not associated with side effects.[15]

Exenatide is commercially available in the USA under the trade name Byetta®.

Exenatide in cats: In healthy cats, exenatide was quickly absorbed after a SQ injection and caused glucose-dependent insulin secretion. Increased glucose tolerance, however, was not observed after a single SQ injection.[16,17] At a dose of 1.0 mcg/kg SQ (about 10 times the dose that is used in diabetic people), exenatide injection did not cause any side effects in healthy cats, except for hypoglycemia in 1 out of 9 cats.[16] Exenatide has led to significant weight loss in healthy cats of 7.0 ± 4.9% (from 4.78 ± 1.5 kg to 4.48 ± 1.5 kg) with a dose of 1.0 mcg/kg SQ BID for 28 days.[17]

Exenatide Extended-Release: A long-acting sustained-release formulation of exenatide (Bydureon®) has recently been approved by the FDA as the first once-weekly subcutaneous injection for treatment of type 2 diabetes people. It consists of injectable microspheres of exenatide and poly(D,L-lactic-co-glycolic acid), a common biodegradable medical polymer with established use in absorbable sutures and extended-release pharmaceuticals, that allows gradual drug delivery at controlled rates. In people, Exenatide plasma concentrations are sustained at an effective concentration (50 pg/mL) for longer than 60 days after a single injection at doses of 5mg, 7mg or 10mg.[18]

It has been shown in a recent clinical study to be more effective than once-a-day insulin glargine in achieving glycemic control with decreased risk of hypoglycemia and with reduction (instead of gain) in body weight.[19] This extended release formulation was also more effective than regular exenatide (Byetta) in achieving glycemic control with no increased risk of hypoglycemia, decreased side effects like nausea, and with similar reductions in body weight.[20]

Exenatide Extended-Release in cats

We have studied Exenatide Extended-Release in healthy cats at a dose of 0.13 mg/kg. Three weeks after a single subcutaneous injection fasting BG was decreased and during a hyperglycemic clamp at that time glucose tolerance improved, insulin concentrations increased and glucagon concentrations decreased. No side effects were observed throughout the study.[21] Exenatide-ER has been compared to placebo in a group of newly diagnosed diabetic cats. There was no difference in the frequency of adverse events between drug and placebo and some metabolic benefits have been attributed to exenatide-ER. Remission rates were not different between groups.[22] This is not entirely surprising considering the fact that newly diagnosed diabetic cats are a heterogeneous group and only some of them have the residual beta cell mass to be able to respond to exenatide. We are currently evaluating the effect of exenatide-ER in cats that are in remission. We are comparing the effect of exenatide-ER to placebo on the duration of remission in this cats, hoping to see long-term maintenance of remission in cats treated with exenatide.

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