INSULIN PREPARATIONS: WHICH ONE AND WHY

Richard W. Nelson, DVM, DACVIM
University of California, Davis

Commercial insulin preparations are typically categorized as rapid acting (e.g., regular crystalline insulin), intermediate acting (e.g., NPH, lente) and long acting (e.g., PZI, glargine, detemir) based on promptness, duration, and intensity of action after subcutaneous administration. NPH and PZI insulin preparations contain the fish protein protamine and zinc to delay insulin absorption and prolong the duration of insulin effect. Lente insulin relies on alterations in zinc content and the size of zinc-insulin crystals to alter the rate of absorption; the larger the crystals, the slower the rate of absorption and the longer the duration of effect. Lente insulin is a mixture of three parts short-acting, amorphous insulin and seven parts long-acting, microcrystalline insulin. Recombinant DNA technology has been applied for the production of insulin analogues with faster and slower absorption characteristics than native human insulin preparations. Rapid-acting insulin analogues include insulin lispro (Humalog, Eli Lilly) and insulin aspart (Novolog, Novo Nordisk). Rapid acting insulin analogues are typically administered three times a day prior to each of the three main meals (breakfast, lunch, dinner), are used to control post-prandial hyperglycemia, and are referred to as prandial insulins. Prandial insulins are not currently used for the home management of diabetes in dogs and cats.

Insulin glargine (Lantus, Aventis Pharmaceuticals) and insulin detemir (Levemir, Novo Nordisk) are long acting basal insulin analogues that have a slow, sustained absorption from the subcutaneous site of insulin deposition, are designed to inhibit hepatic glucose production, are administered once a day at bedtime, and are used in conjunction with rapid-acting prandial insulin analogues in human diabetics. Insulin glargine has been modified to shift the isoelectric point from a pH of 5.4 toward a neutral pH, which makes insulin glargine more soluble at a slightly acidic pH and less soluble at a physiological pH than native human insulin. The solution in the bottle of glargine is acidic which keeps glargine soluble and suspended in the solution, i.e., the solution is clear and the bottle does not need to be rolled prior to drawing up the insulin into the syringe. Because of this dependency on pH, glargine can not be diluted or mixed with anything that may change the pH of the solution. Glargine forms microprecipitates in the subcutaneous tissue at the site of injection from which small amounts of insulin glargine are slowly released and absorbed into the circulation. Insulin detemir is also a long-acting basal insulin analogue in which a fatty acid (myristic acid) is bound to the lysine amino acid at position B29 of the insulin molecule. Prolonged action results from a combination of increased aggregation and albumin binding at the injection site.

Almost all commercial insulin preparations used to treat diabetic dogs and cats are derived from recombinant DNA technology and the insulin mimics the amino acid sequence of native human insulin, hence names like recombinant human NPH and recombinant human PZI. The one exception is purified porcine source lente insulin (Caninsulin® and Vetsulin®, Merck Animal Health). Fortunately, development of insulin antibodies following chronic administration of recombinant human or porcine insulin to diabetic dogs and cats is uncommon and is only

suspected in diabetic dogs and cats that are difficult to control and for which another underlying reason for poor control can't be identified.

Diabetic dogs are reasonably predictable in their response to exogenous insulin. In my opinion, porcine source lente insulin (Caninsulin®) is the initial insulin of choice for treating newly-diagnosed diabetic dogs. Recombinant human NPH insulin is also effective but problems with short duration of effect are common with NPH insulin. Studies to date suggest that the median dosage of lente and NPH insulin required to attain glucose control in most diabetic dogs is approximately 0.5 U/kg/injection, with a range of 0.2 to 1.0 U/kg. One important goal in the initial regulation of the diabetic dog is avoidance of symptomatic hypoglycemia, especially in the home environment. For this reason, my starting insulin dosage is always on the low end of the range, i.e., approximately 0.25 U/kg and I prefer to start with twice a day insulin administration because the overwhelming majority of diabetic dogs require lente and NPH insulin twice a day.

My experience with insulin glargine and recombinant human PZI insulin (ProZinc®, Boehringer Ingelheim Vetmedica) in diabetic dogs has been mixed and somewhat disappointing. My current insulin preference is insulin detemir in poorly-controlled diabetic dogs where lente or NPH insulin is ineffective because of problems with short duration of insulin effect. The most common problem with insulin detemir is a prolonged duration of effect (greater than 14 hours) which can create issues with hypoglycemia and the Somogyi response when insulin detemir is given twice a day. Regardless, most diabetic dogs require insulin detemir twice a day to attain diabetic control, recognizing that the insulin dosage can be quite small to compensate for prolonged duration of effect in dogs with this problem. My initial starting dosage for insulin detemir in diabetic dogs is 0.1 to 0.2 U/kg.

Diabetic cats are notoriously unpredictable in their response to exogenous insulin. There is no single type of insulin which is universally effective in maintaining control of glycemia, even with twice a day administration. Insulin preparations used for the long-term management of diabetic cats include lente, PZI, insulin glargine, and insulin detemir. All have potential problems in diabetic cats; problems primarily resulting from too short or too long of a duration of effect. Recombinant human NPH insulin is consistently and rapidly absorbed following subcutaneous administration but in my experience the duration of effect of NPH insulin is too short in cats to attain diabetic control, even with twice a day administration. I only consider NPH insulin in cats when I am contemplating q 8hr insulin administration to suppress ketone production in cats with recurring ketosis. I do not use NPH insulin for long term home management of diabetes in cats.

Pork-source lente insulin (Vetsulin®, Caninsulin®) is effective for treating and inducing diabetic remission in diabetic cats. Short duration of effect (less than 8 hours) of Vetsulin®/Caninsulin®, even with twice daily administration, is the most common problem with this insulin preparation in diabetic cats; a problem that may result in an inability to attain diabetic control in cats treated with this insulin.

For decades, long-acting beef/pork-source protamine zinc insulin (PZI) has been a popular and effective insulin preparation for treating diabetes in cats in the United States. The current PZI preparation (ProZinc®) is a recombinant human insulin formulation that has been shown to be effective in controlling glycemia and inducing diabetic remission in cats. The most common problem with ProZinc® is a prolonged duration of effect (greater than 12 hours) which can create issues with hypoglycemia and the Somogyi response when ProZinc® is given twice a day.

The insulin analogues insulin glargine and insulin detemir are the longest acting commercially available insulin preparations for treatment of diabetes in humans. Insulin glargine is currently a popular initial insulin choice by veterinarians for the treatment of diabetes in cats. Insulin glargine is effective in controlling glycemia and inducing diabetic remission in diabetic cats. Studies evaluating the efficacy of insulin detemir in diabetic cats have not yet been published. Most of my experiences with insulin glargine and insulin detemir have been in poorly-regulated diabetic cats where Vetsulin® and ProZinc® have been ineffective in improving diabetic control. The duration of effect of insulin glargine has been quite variable, with the glucose nadir occurring as soon as 4 hours and as late as 20 hours after administration in difficult to control diabetic cats. For most cats, the duration of effect has typically been between 10 and 16 hours. My experiences in a limited number of poorly-controlled diabetic cats treated with insulin detemir has been similar to my experiences with insulin glargine, although problems with too long of a duration of effect for twice daily administration seem more prevalent with insulin detemir.

For all of the insulin preparations discussed, I usually start with a low dosage (0.25 U/kg; typically 1 unit per cat) administered q 12h in newly diagnosed diabetic cats, with subsequent dosage adjustments based on the cat's response to treatment and results of blood glucose and serum fructosamine concentrations. In almost all studies to date, the average Caninsulin®, ProZinc®, and insulin glargine dosage that established control of glycemia in diabetic cats was approximately 0.5 U/kg. However, the low end of the effective insulin dosage range was as little as 0.2 U/kg. My primary objectives in the first week of insulin treatment are to have the owner establish a routine for treating their diabetic cat, get the owner comfortable with injecting insulin, avoid symptomatic hypoglycemia, begin to correct the metabolic derangements affiliated with untreated diabetes, and identify those cats that require very small amounts of insulin to control the diabetic state. For these reasons, I always start at the low end of the effective insulin dosage range in newly-diagnosed diabetic cats. Considerable overlap in the insulin dosage range that causes hypoglycemia, establishes control of glycemia, and does not established control of glycemia exists with all insulin preparations. Predicting an effective dosage of any insulin product that does not cause hypoglycemia in some diabetic cats is difficult, in part, because of variability between cats in their response to insulin.