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NEW DEVELOPMENTS IN THE USE OF INSULIN MIXTURES AND ANALOGUES FOR THE PROBLEM DIABETIC

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INTRODUCTION

Despite the fact that diabetes mellitus is one of the most common endocrine disorders in dogs and cats, a poor or inadequate response to insulin is a frequent complaint among many veterinarians and their owners. Clinical signs suggestive of a poor or inadequate response to insulin therapy include recurrence or persistence of clinical signs of diabetes, disorientation or seizures due to hypoglycemia, an insulin dose higher than 2 U/Kg/dose in the dog or > 6 U/dose in the cat, or recurrent ketoacidosis. Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin-induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. In many of these problem diabetics, part of the change in therapy will include a change in insulin type used; in many cases, the solution may be to switch to one of the newer human insulin analogues or insulin mixtures. My goal in this presentation is to present an overview of the commonly used insulin preparation in veterinary practice, as well as to review the newer insulin analogues and mixtures developed for use in human diabetics.

OVERVIEW OF STANDARD AND NEW INSULIN PREPARATIONS

During the past few years, new insulin products have been introduced to the USA, and more insulin products have gained FDA approval and will soon be commercially available. As these new insulins gain popularity, production of old and familiar insulins is being discontinued. Many questions have arisen regarding new insulin products.

The current trend in human medicine is towards long-acting peakless insulin analogue preparations that aim to provide continuous basal insulin supplementation; these long-acting insulin preparations are typically combined with a rapid-onset, short-acting insulin preparation, administered at meal times.^{1,2} This has resulted in many changes in the market for short- and intermediate-acting insulin products and their pre-mixed combinations. It is these products that are most likely to be useful for management of diabetes in dogs and cats, especially if the veterinary insulin preparations prove ineffective or are not available.

STANDARD INSULIN PREPARATIONS AND INSULIN MIXTURES

Porcine Lente Zinc suspension

The only Lente insulin preparation now is **Vetsulin** (trade name in the USA) or **Caninsulin** (trade name elsewhere in the world), manufactured by Merck Animal Health. This is a 40 U/ml porcine insulin zinc suspension specifically registered for veterinary use. There is good evidence that this insulin product is effective for the treatment of diabetes mellitus in dogs and cats.³⁻⁵ Lente insulin has an intermediate duration of action and is a combination of 30% short-acting Semilente insulin and 70% longer-acting Ultralente insulin. It is particularly suited to a twice-daily dosing regimen in diabetic dogs because the meal can be fed at the time of the insulin injection. This more dilute 40 U/ml veterinary preparation is advantageous for small dogs and cats, which might require a total insulin dose of only 1 or 2 U. Dosing is more simple and accurate if specific U-40 syringes are prescribed with this product.

For some time now, availability of Vetsulin in the USA has recently been severely limited by a FDA recall, as a result of their findings that the product may contain varying amounts of crystalline zinc insulin. However, despite the fact that Caninsulin is exactly the same insulin as Vetsulin, Caninsulin was never recalled or withdrawn from the market in any of the countries where it is sold, and it has maintained its reliability during the entire Vetsulin recall period.

The good news is that Vetsulin should be back on the market in this Country soon. Merck Animal Health is working diligently with the FDA to re-introduce Vetsulin to the U.S. market as soon as possible in 2013.

Regular insulin

Products containing 100% regular crystalline insulin (recombinant human insulin) are still available (100 U/ml) and have long been recommended for the management of diabetic ketoacidosis and ketosis in dogs. These include **Humulin R** (Eli Lilly) and **ActRapid** (Novo Nordisk). If these products are withdrawn from the human market, it will be necessary for veterinarians to switch to the newer short-acting insulin analogue preparations, such as insulin lispro or insulin aspart (see below).

Isophane (NPH) insulin

Humulin N (Eli Lilly) and **Novolin N** (Novo Nordisk) are both recombinant human NPH insulin (100 U/ml) that have an intermediate duration of action. The human NPH insulins are effective for the treatment of diabetes in dogs when administered twice-daily.⁶ These recombinant human NPH insulins do not work well in most cats and are NOT recommended.

Combinations of 70% isophane (NPH) and 30% regular insulins

Humulin 70/30 (Eli Lilly) is still available in most countries. This insulin preparation is available as a 100 U/ml pre-mixed combination of 30% short-acting and 70% intermediate-acting insulin. Because it has a similar duration/action curve to Lente insulin (Vetsulin), this insulin is well suited to a twice-daily dosing regimen in diabetic dogs where meals are fed at the same time as the insulin injections. In dogs that do not respond well to Humulin N alone, such combination of NPH and regular insulin may work well.

Recombinant human protamine zinc insulin

Protamine zinc insulin is a recombinant human insulin preparation FDA approved for use in cats. The efficacy of ProZinc (Boehringer Ingelheim) for treatment of diabetic cats is comparable to that of the discontinued beef/pork PZI-VET product.^{7,8} ProZinc is an FDA-approved insulin and is available as a U-40 insulin concentration.

Protamine zinc insulin is not recommended as a first choice therapy for diabetic dogs. In one study evaluating the use of PZI in dogs,⁹ ProZinc insulin was effective in improving or maintaining control of the diabetic state in all the 11 diabetic dogs of that study. However, the median PZI insulin dosage required (0.9 U/kg, bid) was much higher than reported for other insulin preparations in dogs with diabetes. Based on the results of that study, use of ProZinc at a starting dose of 0.5 U/kg, bid, should be considered in diabetic dogs that are poorly controlled because of the short duration of NPH or Vetsulin. The biggest disadvantage of ProZinc for use in dogs (especially larger dogs) is the relatively high cost of injecting the higher doses of insulin needed.

INSULIN ANALOGUES AND ANALOGUE MIXTURES

Rapid-acting Insulin Analogues: Lispro, Aspart, and Glulisine

The "big 3" insulin manufactures of human insulin preparations (Eli Lilly, Novo Nordisk, Sanofi-Aventis) all make their own version of a short-acting insulin analog.

Lispro insulin (Humalog, Eli Lilly) has been shown to be a safe and effective alternative to regular insulin for the treatment of diabetic ketoacidosis in dogs.¹⁰ Engineered through recombinant DNA technology, the penultimate lysine and proline residues on the C-terminal end of the B-chain are reversed. This modification does not alter receptor binding, but blocks the formation of insulin dimers and hexamers. This allows larger amounts of active monomeric insulin to be immediately available for postprandial injections.^{1,2}

Insulin aspart (NovoLog, Novo Nordisk) and **Insulin glulisine** (Apidra, Sanofi-Aventis) are other short acting insulin analogs that could be used as an alternative to regular insulin.^{1,2} Like insulin lispro, these analogues have slight modifications of the insulin structure needed to prevent the formation of hexamers; this leads to larger amounts of active insulin to be available to create a faster-acting insulin. Either insulin aspart or glulisine could potentially be used as an alternative to regular insulin. However, studies in dogs and cats have yet to be reported.

Finally, although not marketed as a short-acting insulin analog, insulin glargine (Lantus) has been reported to have an action profile similar to regular insulin in cats when administered intramuscularly (see below).

Insulin Glargine

Insulin glargine (Lantus, Sanofi-Aventis) is a long-acting synthetic insulin analogue developed for the human diabetic market to provide continuous basal insulin concentrations that inhibit hepatic glucose production.^{1,2} The therapeutic aim is to mimic the physiological pattern of insulin secretion of healthy subjects, and the basal insulin levels provided by these products are supplemented at meal times by administration of short-acting insulin preparations that act during the postprandial period.

Glargine insulin differs from standard insulins because it has been genetically modified, by replacing an asparagine with glycine and adding 2 arginine amino acids to the c-terminal end of the molecule. This alters the pH solubility (isoelectric point) of the molecule, so that it is soluble at a pH 4 but insoluble at neutral pH (e.g., in the body). When glargine insulin is injected into the skin, it precipitates because of the pH change and forms insoluble microcrystals, which are slowly absorbed into the circulation. This constant release of small amounts of insulin prevents major peaks and troughs from developing. The formation of micro-precipitates and slow absorption are dependant on the acidity of glargine. Therefore, glargine cannot be mixed or diluted.

Insulin glargine is efficacious for the long-term treatment of diabetes in cats and is considered the initial insulin of choice by many veterinarians.^{11,12} If improved diabetic control and remission is the goal, insulin glargine must be administered twice daily.

In cats that present with diabetic ketoacidosis, glargine can be used in place of a short-acting insulin such as regular insulin. When glargine is administered intramuscularly or intravenously, it has a similar action profile to regular insulin and can be used in the treatment of cats with diabetic ketoacidosis.¹³ Giving insulin glargine by both the IM and SC route twice daily (70% of the dose given SC and 30% of the dose given IM) can also be used to improve control of the diabetic state in cats with insulin resistance.

Information regarding the use of insulin glargine in diabetic dogs is limited. Initial pharmacological assessment in healthy dogs found that glargine administration resulted in an unpredictable serum insulin concentration response and failed to produce a significant glucose-lowering effect in 2 of 9 dogs after a single injection.¹⁴

However, a recent study found that insulin glargine administered subcutaneously twice daily is a valid method of treatment for naturally occurring diabetes in dogs, and that it is an alternative to other insulin preparations that have been shown to be effective in the treatment of canine diabetes.¹⁵ However, in that study, only 58% of dogs in the present study obtained good control of hyperglycemia, which is less than the reported 75% of dogs with good control in a similar study where a porcine insulin zinc suspension (lente insulin) was used.³ Therefore, although insulin glargine may be an acceptable insulin choice for some dogs with diabetes mellitus, the disease control success rate appears to be lower with glargine than with NPH or lente insulins. Certainly, if a more potent insulin preparation is needed (i.e., in a dog with insulin resistance), detemir insulin would be the insulin of choice, since detemir appears to be at least 4-times more potent than the other insulin preparations which have been evaluated in the dog.¹⁶

Insulin Detemir

Insulin detemir (Levemir, Novo Nordisk) is another synthetic insulin analogue with long duration of action that is produced using recombinant DNA technology.^{1,2} In contrast to glargine, detemir's long duration of action is made possible through modification of the insulin molecule via addition of an acylated fatty acid chain. This modification facilitates reversible binding to plasma proteins, particularly albumin, from where it is released slowly into plasma. The modification also prolongs self-association in the injection depot, which prolongs absorption from subcutaneous tissue at the injection site and contributes to the long duration of action.

In cats, detemir results in a similar action/duration profile and potency to insulin glargine.^{17,18} The remission rates and time to remission for both detemir and glargine are also comparable. A dosing protocol similar to glargine is used, but some cats will require less detemir than glargine (the median dose of detemir was 30% less than glargine in one study of diabetic cats).¹⁸

In dogs, insulin detemir and glargine are in no way comparable.¹⁴⁻¹⁶ Insulin detemir is a very potent, long-acting insulin preparation in dogs, and works much better than glargine in most problem diabetic dogs. In accord with that, we have had success with insulin detemir in dogs with brittle diabetes that were unresponsive to lente or NPH insulins or Humulin 70/30 insulins. In dogs, detemir is dosed initially at 0.1 U/kg BID, administered at time of feeding. This dose is approximately 1/4 of that of NPH or Vetsulin.

Insulin Degludec

Insulin degludec (Tresiba, Novo Nordisk) is a new-generation, ultra-long-acting basal insulin analogue. This latest insulin analogue differs from other long-acting insulin preparations in having a longer half-life, flat time-action profile (less likely to cause hypoglycemia) and less day-to-day variability (less glycemic variability).¹⁹⁻²¹

Degludec is a neutral, soluble ultra-long-acting insulin that forms large soluble multihexamers at the subcutaneous injection site. Its molecular structure is similar to the human insulin amino acid sequence, apart from deletion of Threonine at position B30 and the addition of a 16-carbon fatty diacid attached to Lysine at position B29 via a glutamic acid spacer.

After SC administration, degludec results in the formation of a subcutaneous depot of soluble multihexamers that results in the slow release of insulin monomers into the systemic circulation. Insulin degludec has an onset of action of 30-90 minutes (similar to insulin glargine and insulin detemir). There is no peak in activity, due to the slow release into systemic circulation. The duration of action of insulin degludec is over 42 hours, unlike the 18 to 26 hours provided by current marketed long-acting insulins such as glargine and detemir. The large molecular size of the degludec multihexamers allows for continuous slow release of insulin with less pharmacodynamic variability and within-subject variability than is seen with the currently available insulin analogs.¹⁹⁻²¹

In studies in people with type 1 and type 2 diabetes, degludec was demonstrated to provide similar improvements in blood glucose control as glargine or detemir while also reducing the rate of overall and nocturnal hypoglycemia. One study found that degludec's long duration of action makes it possible to dose the drug at different times each day (i.e., in the morning one day, the evening the next day, the morning the day after that) without sacrificing effectiveness and safety.

Although dosing at roughly the same time each day would make sense for most patients, having the flexibility to vary the time of day when needed could be positive for some patients. In addition, the daily injection time of degludec can be varied to extreme intervals of 24-40 hrs without compromising glycemic control or increasing the risk of hypoglycemia. Therefore, degludec represents an improvement over glargine or detemir that require dosing at the same time each day to maintain sufficient insulin levels in the body and to avoid hypoglycemia.

If all goes according to plan, both degludec and degludecPlus (see below) should be approved in both the US and Europe in the second half of 2012. Obviously, no clinical trials have yet been performed on diabetic cats or dogs. Insulin degludec could potentially provide us with a reliable once-a-day or once-every-other-day therapy for animals with diabetes.

Mixtures of Short-acting and Long-acting Insulin Analogues

The latest insulin preparations released for the human market are pre-mixed combinations of a short-acting insulin analogue with a longer-acting or ultra-long-acting insulin analogue. **Humalog Mix 75/25 (Eli Lilly)** is composed of 70% insulin lispro protamine suspension and 30% insulin lispro injection. This analogue mixture is marketed for human diabetics as an improved product that can be used twice daily in replacement of Humulin 70/30. Compared with Humulin 70/30, Humalog Mix 75/25 in human subjects has a more rapid and predictable onset of glucose-lowering activity, with greater reduction in postprandial glycemia when administered with a meal, and a similar duration of action. **Humalog Mix 50/50** is also available, with half of the insulin being rapid-acting and half being long-acting analogue.

Novolog Mix 70/30 (Novo Nordisk) is composed of 70% insulin aspart protamine suspension and 30% insulin aspart injection. Its onset of action and duration are similar to the Humalog Mix 75/25 described above. **Insulin degludecPlus (Novo Nordisk)** is composed of 70% degludec and 30% insulin Aspart. Although not yet approved for use in the US or Europe, the ultra-long-acting insulin degludec will also be available as a fix-dosed combination of a basal and mealtime insulin.

There is currently no published information on the use of any of these new pre-mixed combinations for the management of diabetes in dogs or cats. These synthetic insulin analogue mixtures appear to have time action/duration characteristics most similar to Humulin 70/30. At least in diabetic dogs, these insulins might be effective when administered twice daily at the same times as meals.

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