

No More Humulin Lente Insulin: What do we use?

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INTRODUCTION

Recently Humulin Lente insulin was taken off the market by Lilly. Since lente insulin is the first choice insulin for many clinicians when treating canine or feline patients with diabetes mellitus, alternative products will be necessary. Current options for an alternative intermediate or long-acting insulin include Vetsulin™, NPH, glargine, and PZI. Since Vetsulin™ is a lente product, this talk will focus on this insulin. Vetsulin™ is the first FDA-approved insulin product for dogs in the US (first approved 4/04), is registered under the trade name Caninsulin™ in 24 other countries. The product was first launched in Australia in 1990. Nine countries currently account for 90% of the product sales (listed in descending order): France, Germany, Italy, Canada, the Netherlands, the United Kingdom, Australia, Belgium and Spain. Eight of these countries not only have a label claim for dogs, but also cats (Germany is pending approval). In total, 23 out of the 24 countries that market Caninsulin™ have both the canine and feline label claims. Over 13 years of clinical experience has demonstrated that Caninsulin™ is successful in the treatment of diabetes mellitus in pets.

NPH INSULIN

NPH insulin is an alternative to lente as an intermediate acting insulin. In most patients (especially cats), it has a shorter duration of action than lente insulin, and there is less optimal control because it usually does not last a full 12 hours. This can result in marked hyperglycemia at the time of insulin administration, and subsequent suboptimal response after injection. However, there is a subset of patients that can be controlled on this insulin.

PZI INSULIN

PZI insulin is classified as long-acting insulin, but is often effective when given every 12 hours. It can be difficult to obtain, is more expensive, and there is variability amongst

different manufacturers (in particular when compounded). Therefore most recommend the use of the Idexx product. When giving this product once daily, glucose curves need to be performed over a 24 hour period. This insulin is mainly useful for cats.

GLARGINE INSLUIN

Glargine insulin (Lantus™) is classified as long-acting insulin, though it is more effective given twice daily to cats. It is a recombinant human insulin analog in a clear aqueous fluid that does not require mixing. The initial dose in cats is 0.5 u/kg bid if the blood glucose concentration is >360 mg/dl and 0.25 mg/kg bid if the blood glucose concentration is < 360 mg/dl (based on ideal, not obese, weight). Many cats will go into remission on this product. It is expensive compared with other insulin products.

VETSULIN™

Vetsulin™ is purified pork insulin. Since pork insulin has an identical amino acid sequence to canine insulin, anti-insulin antibodies are not formed. Vetsulin™ is a lente product, containing 30% amorphous and 70% crystalline, and is therefore classified as an intermediate-acting insulin. The duration of activity of insulin products can be altered by adding components, such as protamine or zinc. Protamine is a large fish protein that can delay the absorption and prolong the duration of the insulin effect. If zinc is used, the absorption rate can be altered depending on the size of the zinc-insulin crystals. Larger crystals slow the rate of absorption, whereas smaller crystals allow faster absorption. Amorphous insulin, which is non-crystalline in structure, may be mixed with crystalline insulin to create a preparation with characteristics of a quick onset combined with activity that has a longer duration.

Vetsulin™ has two peaks of activity in the majority of dogs following subcutaneous administration. The first peak is around 4 hours (due to the amorphous fraction), and the second is around 11 hours (due to the crystalline fraction). The duration of activity varies between 14 and 24 hours. The peak(s), duration of activity, and dose required to adequately control diabetic signs will vary between dogs. In the large multi-center clinical trial (see below), one-third of the dogs were regulated with once-a-day dosing and two-thirds required twice daily dosing. The possibility of once daily dosing is an advantage to some owners of canine diabetics.

It is important that the corresponding insulin syringe is used for each concentration. Using a U-100 syringe (100 IU/ml) with a U-40 insulin product would result in an animal receiving 2.5 times less insulin required. Conversely, if a U-40 (40 IU/ml) syringe were used with U-100 concentration insulin, the animal would receive 2.5 times more insulin, which could have severe undesirable consequences!

CLINICAL TRIAL

A multicenter clinical trial was performed in the United States between May 1997 and May 2001 to evaluate the safety and efficacy of Vetsulin™. The Veterinary Specialty Hospital of San Diego participated in that trial and enrolled the most patients of any site. A total of 66 client-owned dogs were enrolled, and 53 completed the effectiveness and safety field study. The patients completing the study included 22 breeds of purebred and various mixed breed dogs ranging in age from 4.8 to 14 years, and ranging in weight from 4.2 to 51.3 kg. Of the dogs completing the study, 25 were spayed females and 28 were male (21 neutered and 7 intact). All patients were newly diagnosed diabetics or had been on insulin less than eight weeks.

Dogs were started on Vetsulin™ at a dose of 1 IU/kg plus a body weight-dependent dose supplement once daily as shown in Table 1.

Table 1. Body weight-dependent dose supplement to calculate initial dosage of Vetsulin™.

Body Weight	Dose	+ Dose Supplement	Initial Dose
<10 kg (<22 lb)	(Weight in kg) x 1 IU/kg	1 IU	1 IU/kg + 1 IU
10 - 11 kg (22 - 24 lb)	(Weight in kg) x 1 IU/kg	2 IU	1 IU/kg + 2 IU
12 - 20 kg (25 - 44 lb)	(Weight in kg) x 1 IU/kg	3 IU	1 IU/kg + 3 IU
>20 kg (>44 lb)	(Weight in kg) x 1 IU/kg	4 IU	1 IU/kg + 4 IU

The study was divided into two parts, the dose determination period and the study period. The efficacy of any product cannot be established until the appropriate treatment regimen has been determined for each dog. The dose determination period ended when the administered insulin dose and frequency of administration was determined to be appropriate based on adequate control of clinical signs caused by hyperglycemia, and blood glucose curve values. In general, glucose curve values were considered acceptable if the blood glucose concentration remained below 250 mg/dl for 16 or more hours per day, with a nadir of 60 – 160 mg/dl. The end of the dose determination period was considered time 1, which began the study period. Efficacy was evaluated at time 1, time 2 (30±3 days after time 1) and time 3 (60±3 days after time 1). Twelve-hour glucose curves were performed at each of these times. Safety was evaluated throughout the entire treatment period.

The initial treatment time to reach acceptable glycemic control (“Dose Determination Period”) ranged from 5 to 151 days. Dogs were then evaluated for treatment effectiveness three times at 30-day intervals (“Study Period”). The blood glucose curve means and mean nadirs were compared pre- and post-treatment to assess effectiveness.

The blood glucose curve mean was reduced from 370 mg/dL pre-treatment to 151 mg/dL, 185 mg/dL, and 184 mg/dL at the three treatment period evaluations. The blood glucose mean nadir was reduced from 315 mg/dL pre-treatment to 93 mg/dL, 120 mg/dL, and 119

mg/dL at the three treatment period evaluations. Sixty days after an adequate Vetsulin™ dose was initially established, 94%, 96% and 83% of study dogs experienced a reduction in polyuria, polydipsia, and ketonuria, respectively. There was adequate glycemic control an average of 81% of the time during the “Study Period”. An important finding was that 34% of the dogs were controlled on once daily administration at the end of the 60-day study period. The injection frequency and effective dose range for dogs varied substantially as shown in Table 2.

Table 2. Injection frequency and dosage range in dogs receiving Vetsulin™

Study Time	Dogs on SID therapy	Dogs on BID therapy	Range of SID doses (IU/kg)	Range of BID doses (IU/kg)	
				a.m. dose	p.m. dose
Time 0 (Initial dose)	51 (96%)	2 (4%)	0.94 - 1.28	1.06 - 1.07	1.06 - 1.07
Time 1	23 (43%)	30 (57%)	0.44 - 2.22	0.39 - 1.29	0.39 - 1.26
Time 2	23 (43%)	30 (57%)	0.33 - 2.19	0.40 - 1.25	0.39 - 1.22
Time 3	18 (34%)	35 (66%)	0.43 - 2.18	0.34 - 1.40	0.28 - 1.40

In this clinical effectiveness study, dogs received various medications while being treated with Vetsulin™ including antimicrobials, NSAIDs, thyroid hormone supplementation, internal and external parasiticides, anti-emetics, dermatological topical treatments and oral supplements, and ophthalmic preparations containing antimicrobials and anti-inflammatories. No medication interactions were reported. This drug was not studied in dogs receiving steroids.

CONCLUSION

Vetsulin™ has several advantages: 1) it is currently the only FDA-approved veterinary-labeled insulin product; 2) being a purified pork product, it has an amino acid sequence identical to canine insulin; 3) there are published data in dogs (*Journal of Small Animal Practice* 1997; 38:434-438 and *Australian Veterinary Journal* 2000; 78:831-834; the United States multicenter clinical trial was recently submitted for publication); 4) approximately one-third of dogs can be controlled on once daily administration; 5) since the product is a U-40 insulin (40 units/ml), more accurate dosing can be achieved in small patients without further dilution; 6) there is over 14 years of international safety and efficacy history; and finally 7) this product will allow the veterinarian to enter the canine insulin market.

More information about Vetsulin™ can be obtained on the website: www.vetsulin.com.