Use of ultralente insulin in cats with diabetes mellitus

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Protamine zinc insulin (PZI) has been one of the primary insulins recommended for treatment of insulin-dependent diabetes mellitus (IDDM) in cats. Unfortunately, the manufacturer[a] discontinued production and distribution of PZI in December 1991, thereby forcing veterinarians to use other types of insulin for management of diabetic cats. Currently, there are five commonly used insulins available to veterinarians. They can be categorized by their kinetic properties (ie, time for onset of action and duration of effect; Table 1). Except for the regular type, all insulins are modified to delay absorption from a subcutaneous depot. Such modification results in slow action of extended duration. These modifications are made by addition of zinc, protamine, or both to insulin suspended in a suitable buffer.[1]

The lente group of insulins was introduced and marketed in 1952.[2] These insulins rely on alterations in zinc content and size of zinc-insulin crystals to alter the rate of absorption from the subcutaneous site of deposition. The larger the crystals, the slower the rate of absorption and the longer the duration of effect. The lente insulins do not contain any foreign protein (ie, protamine). Semilente insulin is a short-acting, amorphous preparation, with duration of activity that is slightly longer than that of regular crystalline insulin. Ultralente insulin is a microcrystalline, long-acting preparation. Lente insulin is a mixture of 3 parts semilente and 7 parts ultralente insulin. Lente insulin is an intermediate-acting preparation. The long-acting ultralente insulin would seem the natural substitute for PZI.

Extremely pure insulin (ie, little to no proinsulin or other foreign protein) can be harvested from several sources. For ultralente insulin, sources include beef[b] and a combination of beef and pork.[c] More recently, recombinant-DNA human ultralente insulin[d,e] has been produced.[1] The amino acid sequence of feline insulin is most similar to that of cattle.[3] The antigenicity of the various species of insulin and the potential for insulin resistance attributable to insulin antibody formation in cats is unknown. When insulin ineffectiveness attributable to excess insulin binding by antibody is suspected, beef-source ultralente insulin[b] or recombinant human ultralente insulin[d,e] may be used.

Table 1—Characteristics of market insulins and actions in diabetic cats

Action/type	Added protein	Zinc content (mg/100 U)	Action (h)*	
			Peak	Duration
Rapid				
Regular (crystalline)	None	0.01 to 0.04	1 to 5	4 to 10
Semilente	None	0.2 to 0.25	1 to 5	4 to 10
Intermediate				
Isophane (NPH)	Protamine†	0.02 to 0.04	2 to 8	4 to 12
Lente	None	0.2 to 0.25	2 to 10	6 to 16
Long				
Ultralente	None	0.2 to 0.25	4 to 12	7 to 18
Protamine zinc	Protamine†	0.2 to 0.25	3 to 12	6 to 18

*Approximate ranges based on clinical impressions in cats with insulin-dependent diabetes mellitus. There is considerable variation from cat to cat and from time to time in the same cat. †NPH insulin contains 0.5 mg and protamine zinc contains 1.25 mg, respectively, of protamine/100 U.

In treating cats with newly diagnosed IDDM, beef/pork-source ultralente insulin is recommended at initial dosage of 1 to 3 U/cat, in a single morning injection. Cats may be hospitalized for 24 to 48 hours after initiating insulin therapy to monitor them for hypoglycemia or they may be treated by their owners for 4 to 7 days before intensive monitoring is begun. Blood glucose concentration is then assessed every 1 to 2 hours from 8 AM to between 4 and 6 PM . Insulin dose is decreased if hypoglycemia (ie, blood glucose concentration < 80 mg/dl) is identified, or dose is increased by 0.5 to 1 U if all glucose concentrations are > 250 mg/dl. Subsequent evaluations are performed every 7 to 14 days until glycemic control is established. Owner opinion, results of physical examination, body weight, and blood glucose concentration

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[a]Eli Lilly Co, Indianapolis, Ind.

[b]Ultratard, Novo Nordisk Pharmaceuticals Inc, Princeton, NJ.

[c]Ultralente Iletin I, Eli Lilly Co, Indianapolis, Ind.

[d]Humulin U, Eli Lilly Co, Indianapolis, Ind.

[e]Ultratard HM, Novo Nordisk Pharmaceuticals Inc, Princeton, NJ.

(measured every 1 to 2 hours for 8 to 12 hours) are used to assess insulin therapy at each evaluation.

When initially substituting ultralente for PZI insulin, change in dose or frequency of administration is not recommended. The ultralente insulin dose that results in glycemic control may be quite different from the PZI insulin requirement. Most diabetic cats we treated required slightly more ultralente insulin to obtain similar glucose-lowering effect. However, in some cats, the ultralente insulin dose has been the same or less than the PZI insulin dose. When converting from PZI to ultralente insulin, cats must be reregulated, beginning with evaluation of insulin therapy 4 to 7 days after initiating ultralente insulin administration.

The ideal goal of insulin therapy is to maintain blood glucose concentration between 100 and 250 mg/dl. Mean (± SD) ultralente insulin dosage to attain this goal in recently treated cats was 0.5 ± 0.2 U/kg of body weight/injection. Most of our cats require administration of ultralente insulin twice a day to maintain glycemic control. However, variation exists in effectiveness (ie, ability to lower the blood glucose concentration), onset of action, time of glucose nadir, and duration of action (defined as the time from insulin injection to the first blood glucose concentration > 250 mg/dl after the glucose nadir) of ultralente insulin. Average onset of action is 3 hours (range, 1 to 10 hours), the glucose nadir typically is observed 7 hours (range, 4 to 12 hours) after insulin administration, and the duration of action has been 7 to 18 hours in our diabetic cats.

The most common problem associated with ultralente insulin in cats is ineffectiveness in lowering the blood glucose concentration. Some diabetic cats absorb ultralente insulin from the subcutaneous site of deposition too slowly for it to be effective in maintaining acceptable glycemic control. In these cats, blood glucose concentration may not decrease for as long as 6 to 10 hours after the injection or, more commonly, blood glucose concentration decreases minimally despite dosage of 8 to 12 U/cat given every 12 hours. As a consequence, blood glucose concentration remains > 300 mg/dl for most of the day, with resultant polyuria and polydipsia. When ultralente insulin dosage exceeds 8 to 10 U/cat given every 12 hours with minimal decrease in blood glucose concentration, one must consider substituting another insulin. Successful strategies have included beef/pork-source lente,[f] recombinant human lente[g] and beef/pork-source NPH[h] insulins at initial dosage of 3 to 4 U/cat given every 12 hours. The preceding 3 insulins are listed, subjectively, in order of increasing potency. For many cats, conversion to an intermediate-acting insulin is effective in improving glycemic control. Clinicians must also consider other causes for insulin ineffectiveness, such as persistent stress-induced hyperglycemia, posthypoglycemic rebound hyperglycemia, concurrent illness (eg, infection, pancreatitis), diabetogenic medications, and excess circulating insulin-binding antibodies.[4] Lastly, on any given day, blood glucose concentration may not be typical for that cat given that type of insulin at that dose. Therefore, owner opinion, results of physical examination, and body weight must be included in all decisions.

[f]Lente Iletin I, Eli Lilly Co, Indianapolis, Ind.
[g]Humulin L, Eli Lilly Co, Indianapolis, Ind.
[h]NPH Iletin I, Eli Lilly Co, Indianapolis, Ind.

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