FELINE DIABETES MELLITUS: WHICH INSULIN DO I CHOOSE & HOW DO I ADJUST THE DOSE?

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MANAGEMENT OF FELINE DIABETES

Therapy for diabetes should be instituted as soon as possible after diagnosis. The aims of therapy are to treat any underlying disease, and achieve good glycemic control. Administration of insulin and dietary modification are the principal therapies used for management of diabetic cats. Oral hypoglycemic drugs may be useful in some cats.

Cats that are not substantially dehydrated and are still eating should be treated with subcutaneous insulin. Cats initially presented with diabetic ketoacidosis can be treated with subcutaneous insulin after stabilization. Because clinical hypoglycemia can be life-threatening, avoid aiming for perfect glycemic control if using lente insulin. The use of longer-acting insulins and low carbohydrate diets facilitates achieving better glycemic control while minimizing the chance of hypoglycemia

Insulin therapy

Insulin therapy remains the preferred initial and long-term treatment of choice for diabetes mellitus in cats. Its effectiveness and safety may be enhanced when combined with oral hypoglycemic agents and dietary therapy.
Many types of insulin are available and have been used in cats. Achieving good glycemic control with intermediate acting potent insulins such as NPH, lente and ultralente is often difficult, and increases the risk of clinical hypoglycemia. Recent data indicates that the long-acting insulins such as glargine or determir provide better glycemic control and reduced risk of clinical hypoglycemia when given twice daily and combined with a low carbohydrate diet. Of the insulins available that have been studied in cats, glargine or detemir appear to be the insulin of choice.

Oral hypoglycemic drugs

The use of oral hypoglycemic drugs to treat feline diabetes has been limited for a number of reasons. Many owners find administering tablets more difficult than injecting with insulin. Drugs which stimulate insulin secretion (eg. sulphonylureas) require adequate beta cell function to be effective, and if there is inadequate glucose-lowering effect, persistent hyperglycemia can lead to continued beta cell loss through glucose and lipid toxicity. These drugs may also stimulate accelerated islet amyloid deposition exacerbating beta cell loss. The probability of remission is significantly lower for sole treatment with oral hypoglycemic drugs compared with using a long-acting insulin.

Monitoring therapeutic efficacy

Response to treatment can be evaluated in a number of ways, and no individual modality should be used as the sole parameter for adjusting therapy. A combination of owner assessment, clinical signs, and changes in body weight and water intake are often the best indicators of glycemic control. Dosage changes can be made based on a number of different blood glucose parameters, and optimally should include more than one parameter. The pre-insulin glucose concentration is important when using glargine, detemir and PZI, as there is often a persisting effect from the previous injection. Nadir (lowest) glucose concentration can be used for dosage adjustment in a similar way it is used with other insulin types. Water drunk and urine glucose concentration are probably more important when using glargine than for other types of insulin, and is discussed below.

When using other insulins (eg lente or NPH), dosage changes are usually based on nadir blood glucose. Pre-insulin glucose, time to nadir and the time to return to baseline are also used where appropriate, and recommendations for their use are listed in table 2. Water drunk, urine glucose and clinical assessment may be less important for making dosage changes with these insulins, but should still receive consideration when adjusting dosage.

Table 1: Parameters for changing insulin dosage and frequency based on blood glucose measurements when using lente or NPH in diabetic cats.
Adapted from: Rand JS, Marshall R: Diabetes mellitus in cats. Vet Clin North Am Small Anim Pract 35[1]:211, 2005.

Blood Glucose **Variable**	**Recommendation**
If pre-insulin blood glucose concentration is <210mg/dL (< 12mmol/L)	With-hold insulin and check for diabetic remission
If pre-insulin blood glucose concentration is 211-250mg/dL (13 - 16mmol/L)	Total dose should be no more than 1U/cat bid
If nadir blood glucose concentration is < 54mg/dL (<3mmol/L)	Dose should be reduced by 50 %
If nadir blood glucose concentration is 54-90mg/dL (3 – 5mmol/L)	Dose should be reduced by 1U if poor control of

	clinical signs of diabetes; dose should remain the same if exemplary control of clinical signs
If nadir blood glucose concentration is 91-180mg/dL(6 – 9mmol/L)	Dose should remain the same
If nadir blood glucose concentration is >180mg/dL(> 10mmol/L)	Dose should be increased by 1U
If nadir blood glucose concentration occurs within 3 hours of insulin administration, or blood glucose returns to baseline within 8 hours	Change to longer acting insulin (ie. Glargine, detemir or PZI)
If the nadir blood glucose concentration occurs at 8 hours or later	Once daily administration may be used, although twice daily administration at a reduced dose is preferred

Glargine

Glargine is a human synthetic insulin analogue produced by recombinant DNA technology utilizing *E.Coli.* It differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the B-chain terminus. Glargine is a clear aqueous solution in 100U/ml vials with pH=4 until injected subcutaneously. The interaction of the acidic insulin and the relatively neutral pH of the subcutaneous tissues forms micro-precipitates, and has a relatively constant systemic absorption profile. The formation of micro-precipitates and slow absorption are dependant on the acidity of glargine, hence glargine cannot be mixed or diluted.

Glargine is marketed for human patients as a very long-acting "peak less" insulin, with regard to its glucose lowering effects. It is designed to provide a basal or background insulin concentration, with the intention that a shorter-acting insulin be administered at meal times to achieve optimal glycemic control. Insulin glargine gained approval from the United States Food and Drug Administration in June 2000, for use in treating type 1 and type 2 diabetes in humans. The expected benefits in diabetic cats of an insulin preparation with a longer duration of action include improved glycemic control resulting in increased rates of diabetic remission, reduced rates of euthanasia, and decreased cost to clients.

The pharmacokinetics and pharmacodynamics of once daily administration of glargine compared with two of the most commonly used insulin preparations, porcine lente and protamine zinc insulin (PZI), has been reported in healthy cats. Once daily administration of glargine was found to have a similar mean daily glucose concentration and area under the 24hr glucose curve to PZI, and both were significantly lower than lente insulin. Glargine produced a glucose nadir later than PZI or lente, and had longer duration of action than lente. The duration of action for glargine was 23$\pm$0.9hrs, and 7 of the 9 cats had significantly decreased blood glucose concentration at 24hrs.

The administration of glargine once daily versus twice daily has also been compared in healthy cats. While once daily administration of insulin glargine at 0.5U/kg provided a significant blood glucose lowering effect, a longer effect was achieved by administering glargine at 0.25U/kg BID. When using glargine in diabetic cats, we have found that most cats may be maintained on once daily injections of glargine, but superior glycemic control is achieved if insulin is injected twice daily. This is of particular importance in newly diagnosed cats in which prompt good glycemic control may result in remission, hence the recommendation for BID dosing in new diabetic cats.

The usefulness of glargine for treating newly diagnosed diabetic cats has been evaluated. Twenty-four newly diagnosed diabetic cats (17m,7f) were treated with either glargine, PZI or lente (n=8 for each group) and fed a very low carbohydrate-high protein diet (Purina DM canned). Insulin was initially given at 0.5U/kg BID S/C if blood glucose was >360mg/dl, and 0.25U/kg BID S/C if blood glucose was <360mg/dl. Insulin dose was then adjusted based on serial blood glucose curves and water intake. Cats were defined as achieving diabetic remission if normoglycemia was maintained without insulin therapy for more than 2 weeks.

At diagnosis, there was no statistical difference between treatment groups for age, body weight, body condition score, or concentrations of fructosamine, blood glucose, B-hydroxybutyrate or bicarbonate.

Glargine treated cats had lower 12hr glucose concentrations after 17 days, than those treated with PZI or lente. Mean 12hr blood glucose at 4 weeks was significantly lower for glargine than PZI and lente treated cats. Fructosamine concentration after 4 weeks of treatment was significantly lower than at diagnosis for glargine treated cats but not for PZI or lente.

All 8 cats treated with glargine went into diabetic remission within 4 months of beginning treatment, while 3 cats treated with PZI and 2 cats treated with lente achieved diabetic remission.

Only 1 cat treated with glargine required an increase in insulin dose above 0.5U/kg BID, and 7 of 8 cats had their insulin dose reduced in the first 3 days of treatment. This is an important factor when initiating treatment with glargine, as there is usually a carry-over effect from the previous dose that may take several days to become apparent.

A significant finding in this trial was that no cat treated with glargine showed clinical hypoglycemia despite having biochemical hypoglycemia, while 2 cats treated with lente and 1 cat treated with PZI insulin exhibited signs of clinical hypoglycemia.

Glargine can be safely instituted at 0.5U/kg bid and serial blood glucose curves should be obtained daily for 3 days either in hospital or at home. When evaluating the blood glucose curve using glargine, it is often more useful to assess pre-insulin glucose concentration rather than the nadir glucose. We have found it often takes 3-5 days for a good glucose-lowering effect to be seen in the glucose curves, possibly because of the long duration of action and carry-over effect of glargine. Many cats will need to have their initial dose reduced within 2 weeks and many will achieve remission within 4 weeks.

Monitoring and adjusting insulin dose when using glargine should be based on a number of parameters including; pre-insulin and nadir glucose concentration, water intake, urine glucose concentration and clinical assessment as shown in Table 2. We have found pre-insulin glucose concentrations measured at home an excellent tool for well-educated owners to safely modify daily doses of glargine. Cats treated with glargine should have a negative, 1+ or 2+ urine glucose (scale 0-4+) and a value of 3+ or 4+ likely indicates that a dose increase is required.

The good glycemic control when using glargine likely reverses glucose toxicity of the B-cells, which facilitates endogenous insulin production and a reduced requirement for exogenous administration. Insulin dose may be reduced sequentially as indicated by blood glucose concentration, urine glucose and water intake until the dose is 1U SID. Even if normoglycemic, it is recommended that insulin is not withdrawn within 2 weeks of commencement of therapy. Sequential deduction of insulin dose to 1/2 U SID is recommended before insulin is withdrawn, and the cat carefully monitored afterwards to ensure remission has continued. It is also imperative that cats remain on a low-carbohydrate diet with calorie control to prolong the remission period. It is the authors' experience that newly diagnosed diabetic cats that have good glycemic control within the first few weeks of therapy, are very likely to

go into diabetic remission. Cats that have been long-term diabetics are less likely to go into remission probably because of progressive B-cell loss.

It is the authors' conclusion that glargine is safe and effective in treating feline diabetes and is the preferred insulin in newly diagnosed diabetic cats. Long-term diabetic cats should be changed to glargine if there is poor glycemic control or owners wish to pursue once daily injections. High remission rates are expected in newly diagnosed cats when combined with a low-carbohydrate diet and twice daily injections.

Table 2. Parameters for changing insulin dosage when using insulin glargine or PZI in diabetic cats.

Parameter used for dosage adjustment	**Change in dose**
If pre-insulin blood glucose concentration >216mg/dL (>12mmol/L) ***and/or*** If nadir blood glucose concentration >180mg/dL (>10mmol/L)	Increase by 0.25-1U Use water drunk and urine glucose as a guide to dose change
If pre-insulin blood glucose concentration 180<216mg/dL ($\geq$ 10 - $\leq$12mmol/L) ***and/or*** nadir blood glucose concentration is 90-160mg/dL (5-9mmol/L)	Same dose
If nadir glucose concentration is 54-72 mg/dL (3-4 mmol/L).	Water drunk, urine glucose and next pre-insulin glucose concentration to determine if insulin dose is decreased or maintained.
If pre-insulin blood glucose concentration <180mg/dL (10 mmol/l) ***and/or*** If nadir blood glucose concentration < 54mg/dL (<3 mmol/l)	Reduce by 0.5- 1U ***or*** if total dose is 0.5-1U SID or less, stop insulin and check for diabetic remission
If clinical signs of hypoglycemia are observed	Reduce by 50%
In fractious cats where blood glucose measurement is not possible, use water drunk and urine glucose to adjust dose. However, glycemic control will likely be inferior, and remission delayed or not obtained	
If water intake is <20mls/kg on wet food or <60mls/kg on dry food	Same dose
If water intake is >20mls/kg/24hr on wet food or >60mls/kg/24hr on dry food	Increase dose by 0.5-1U
If urine glucose is $\geq$ 2+ (scale 0 - 4+)	Increase dose by 0.5-1U
If urine glucose is negative	Reduce dose every 2 weeks by 0.5-1 U. Check for diabetic remission if dose is 0.5-1U SID

KEYWORDS, feline diabetes, diabetic remission, insulin, glargine

Suggested reading:

Selected articles are available our website: www.uq.edu.au/ccah

Rand JS and Marshall RD Diabetes mellitus in cats. Vet Clin North Am Small Anim Pract 35[1]:211-24 2005

REFERENCES AVAILABLE ON REQUEST