Proceeding of the NAVC
North American Veterinary Conference
Jan. 8-12, 2005, Orlando, Florida

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NEW CONCEPTS IN MANAGING DIABETIC CATS

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INSULIN THERAPY

Managing diabetics can be frustrating. In order to minimize the stress to veterinarians, owners and patients, the “best” insulin is sought. Until recently, there were 5 main forms of insulin available on the market: Lente, NPH, PZI, Ultralente and regular. However, no one insulin was the best. In one study in cats, for example, no significant difference was found in glycemic control among cats treated with PZI, Ultralente or Lente. In general, which insulin to start with is a matter of personal preference and experience. In addition, some patients will not respond to one insulin but will respond well to another, e.g. 20% of cats do not respond to high doses of Ultralente insulin but will be effectively managed by twice-daily Lente. Therefore, if one insulin does not work, another should be tried.

One study has assessed the PZI available from Idexx. Sixty-seven privately owned diabetic cats were used, of which 34 were newly diagnosed, 32 were being treated with insulin and 1 was receiving glipizide. The cats were studied for 45 days. Initial dosage of PZI ranged from 0.2-0.6 U/kg BID. At the end of the 45 days, mean dose was 0.9 U/kg (range 0.2-1.8). Mean blood glucose nadir occurred approximately 5-7 hrs after insulin injection, but ranged from 1-9 hrs.

Overall, 90% of owners believed their cat improved. Clinical hypoglycemia occurred in 5 cats and hypoglycemia without clinical signs occurred in another 21 (31%). Ten cats were not controlled by day 45. Whether longer treatment and more dosage adjustment would have achieved control is unknown. In general, cats with newly diagnosed diabetes had a better response than those cats with previously treated diabetes; perhaps the cats that failed previous treatment had an underlying cause of insulin resistance.

Most diabetic cats will require PZI BID for adequate control, but once-daily injections may suffice in up to 25%. Initial PZI dosage should be low (e.g. 1 U/injection) to avoid hypoglycemia. Information has been presented recently regarding the use of a new human synthetic insulin analogue called insulin glargine in healthy and diabetic cats. Insulin glargine is produced by recombinant DNA technology. The chemical structure of insulin glargine has been altered slightly from native human insulin. Glargine is a clear aqueous solution in 100U strength with a very acidic pH (pH=4). When insulin glargine is injected subcutaneously into a more neutral pH, the insulin forms micro-precipitates with a supposedly relatively constant absorption into the systemic circulation. The micro-precipitate formation and slow absorption are dependent on the pH of the glargine, so glargine cannot be mixed with other insulins or diluted.

In healthy cats, insulin glargine was compared to Lente and PZI. In comparison to PZI and Lente, glargine peaked later, but there was no difference in the nadir blood glucose concentration. Comparing SID to BID administration of glargine in healthy cats, there was no difference in time to onset of action, nadir glucose concentration or time to reach nadir glucose. Not surprisingly, however, time for glucose to return to baseline was significantly longer for BID than SID.

In diabetic cats, the use of glargine appears extremely promising. Glargine has a very long duration of action and a predictable blood glucose lowering effect. In 6 newly diagnosed cats treated with a high protein-low carbohydrate diet (Purina DM canned), the diabetes resolved in all within 4 months. It should be noted that 4 of the cats were Burmese cats, and the pathophysiology of diabetes in this breed may differ from that in most cats. For this reason, it may be that resolution of diabetes is more likely in Burmese cats. In any case, glargine appears to be a very good insulin to use in any cat giving control of blood glucose concentrations throughout most of the day. Long-term diabetic cats have been switched to and treated with glargine as well with good success, but the diabetes has not resolved. Cost-wise, insulin glargine is comparable to PZI from Idexx.

Recommendations are to start cats on glargine at 0.25 or 0.5 U/kg SQ if their blood glucose concentration is <360 mg/dl or >360 mg/dl, respectively. In either case, BID administration is recommended. Since the doses are small, low-dose 0.3 ml syringes should be used for accurate dosing. For the first 3 days, 12-hr blood glucose curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the blood glucose curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. The insulin dose should not be increased for the first week no matter what the curves look like!!! After the first 3 days, the cat should be sent home and should then return for a curve 7 days later. Subsequent blood glucose curves should be performed at 1, 2 and 4 weeks and then as required.

If at recheck, the pre-insulin blood glucose concentration is >360 mg/dl and/or the nadir concentration is >180 mg/dl, the glargine dose should be increased 0.5 U/cat. The dose should not be changed if the pre-insulin blood glucose concentration is 240-360 mg/dl and/or the nadir concentration is 90-180 mg/dl. The dose should be decreased 0.5 U/cat if the pre-insulin blood glucose concentration is <180 mg/dl or decreased by 1.0 U/cat if the nadir concentration is <54 mg/dl. If clinical signs of hypoglycemia are present, the glargine dose should be decreased 50%. Administration of glargine insulin should not be discontinued within 2 weeks of starting treatment regardless of the curve – decrease the dose if needed, but do not stop the insulin (J. Rand, personal communication).

If performance of a curve is impossible due to temperament or financial issues, start insulin glargine at 2 U/cat SQ BID and have the owner monitor urine glucose concentration or water intake. A cat well-regulated on glargine should have trace urine glucose at most, and urine glucose should be negative most of the time. If after 2 weeks of receiving glargine insulin, urine glucose is > trace, the dose should be increased 1 U/cat/wk until urine glucose is negative or water intake is <20 ml/kg/24h if eating canned food or <70 ml/kg/24h if eating dry food. At this point, keep the cat on the same dose for 2 weeks then start decreasing the dose by 1 U/cat/wk until urine glucose is positive or the insulin has been discontinued (J. Rand, personal communication).

Although hypoglycemia was not documented in 6 diabetic cats treated with glargine, in 1/3 of normal cats treated BID, mean blood glucose concentration remained significantly suppressed at 24 hrs, indicating a carryover effect of glargine. Therefore, hypoglycemia is a possibility and should be monitored for as when using any other type of insulin.
The site of insulin injection is another important aspect to consider. An appropriate location for an injection site must be chosen, as absorption of insulin from various sites in the body differs. For example, in humans, insulin absorption from the abdomen is more rapid than from the thigh, and injection into an extremity may result in inconsistent insulin absorption depending on exercise and limb movement. In dogs and cats, the dorsal neck or scruff has commonly been used as a site for injection, but this site may not be ideal due to low blood flow and increased fibrosis caused by repeated injections. A better option may be to administer the insulin at sites along the lateral abdomen and thorax. The chosen area should be rotated daily in order to prevent fibrosis at an injection site.9

**DIETARY MANAGEMENT**

Through unknown mechanisms, dietary fiber can delay gastrointestinal glucose absorption, reducing post-prandial fluctuations in blood glucose and enhancing glycemic control. High fiber diets have been traditionally recommended for diabetics but this is now being questioned. Insoluble fiber, the type present in commercial feline high fiber diets, can improve glycemic control in diabetic cats.9 However, recent theories suggest that high carbohydrate diets may lead to DM in cats and that high protein may be beneficial. A number of cats on a high protein, low-carbohydrate diet (e.g. Hill’s M/d, Purina DM, Hill’s growth canned) had their diabetes resolve or experienced a marked reduction in insulin dose.10-12

**MONITORING**

Recent emphasis has been placed on finding better monitoring methods. Performance of in-hospital blood glucose curves has long been the gold standard for assessing diabetic control, but they are certainly not perfect. Blood glucose curves can be affected by the stress of hospitalization and deviation from normal routine. One study recently assessed day-to-day variability of serial blood glucose concentration curves in diabetic dogs.13 Glucose curves were performed on 2 consecutive days and all conditions were identical on the 2 days, e.g. type and dose of insulin, amount and type of diet, etc. Parameters such as minimum blood glucose concentration, mean blood glucose concentration, fasting blood glucose concentration before the morning injection or before the evening injection (all dogs were treated BID), time from insulin injection to nadir and maximum blood glucose concentration were significantly different between the 2 curves. In some dogs, the curve showed better control on day 1 while in others it was day 2. To examine the clinical implications of any day-to-day variability of the serial curves, a theoretical recommendation for adjustment of the dog’s insulin dose was based on the results of each curve. Thirty sets of paired 12-hour curves lead to opposite theoretical recommendations for adjustment of a dog’s insulin dose on day 2 compared to day 1 in 27% of occasions. For 17% of the curves, a different but not opposite recommendation resulted. The same recommendation for dosage adjustment on both days was made in 57% of the paired curves.15

One point made by this study is that the time of the blood glucose nadir can vary greatly from day to day. It is important to always perform serial measurements to ensure that the nadir is not missed. Predicting the timing of a diabetic’s nadir on the basis of previous serial blood glucose curves and obtaining a single sample at that time is unlikely to give a reliable result.13

In order to avoid some of the problems associated with in-hospital curves, performance of glucose curves at home has taken on new importance. For home glucose curves, it is not necessary for venous blood to be collected. Capillary blood is suitable.14 and the ear is the best site for blood collection. Two types of lancing device are available. If using conventional automatic devices designed for pricking human fingertips, a device with a variable needle depth should be chosen. The appropriate depth for each patient can then be used.15 Warming of the ear with a hair dryer or a warm, wet washcloth enclosed within a plastic bag may be necessary but not well tolerated, and it may take up to 2 minutes to obtain an adequate sample.16 A device which creates a vacuum after lancing the skin (e.g. Microlot Vaculance, Bayer) does not require warming of the ear and generates an adequate drop of blood within approximately 30 seconds,15 but mastery may be a bit difficult and require repeated instruction.14 Glucometers that require minimal amounts of blood as well as those that “sip” the blood into the strip are desirable.

Continuous monitoring of glucose concentrations has also received attention of late.16,17 The CGMS (Continuous glucose monitoring system, Minimed) is a device that can be strapped onto a patient and a small needle inserted into subcutaneous tissue. Interstitial glucose concentrations are sampled every 5 minutes for up to 72 hrs. Using such a device gives many more data points for evaluation and avoids the stress of multiple venipunctures or catheterization. A patient at home could potentially wear the device as well. The device has been assessed in normal and diabetic dogs and cats. Interstitial and serum glucose concentrations were highly correlated overall.16,17 The working range of the CGMS is approximately 40-400 mg/dL, i.e. blood glucose concentrations outside the range cannot be measured. In certain cases, post-prandial increases in serum blood glucose concentration were not detected in the interstitial fluid.17 Some variation existed between patients and the differences between serum and interstitial glucose concentrations were more marked in some patients than others. The greatest discrepancies occurred at higher glucose concentrations.17 No irritation resulted from sensor placement.16,17

To examine the clinical implications of using the CGMS in one study, 2 clinicians independently reviewed CGMS traces and glucometer-generated blood glucose curves in 10 diabetic dogs and made recommendations regarding the insulin dose and frequency. The same change of insulin dose was recommended 5 of 10 times by clinician A and 7 of 10 times by clinician B. The same adjustment of frequency of insulin administration was recommended 6 of 10 times by clinician A and 8 of 10 times by clinician B. This suggests that the data generated by the CGMS is useful for clinical management of insulin therapy, at least in diabetic dogs.17 In the cases where a different recommendation was made, it was not determined which was the better – the one based on glucometer data or the one based on CGMS data.

Measurement of serum concentrations of the glycated proteins GHB and fructosamine can also be helpful, but are not perfect. Although a trend exists that the less poorly controlled the diabetes, the higher the serum concentration of either glycated protein is likely to be, this is not absolute. Poorly controlled diabetics can have normal concentrations of either protein and, conversely, well-controlled diabetics can have very high concentrations of either.18,19 In one study, only 16% of serum GHB concentration and 20% of serum
fructosamine concentrations were within reference range in well-controlled dogs. Current recommendations are to aim for a value slightly above normal as the belief is that diabetic animals with normal glycated protein concentrations are more prone to hypoglycemia. In addition, measurement of glycated proteins alone is probably not adequate for assessment of overall control. Alternatively, the best use for these may be as one more piece of information where conflicting data exist or, if measured at each recheck, to evaluate trends in glycemic control.

Recently, home monitoring of clinical signs alone has been advocated as an accurate method of diabetic assessment. In one study of 53 dogs, control was judged to be good or bad based on clinical signs, physical examination findings and body weight. The clinical determination of good or poor control was compared with fasting blood glucose, serial blood glucose curve and serum fructosamine and GHb concentrations. Although all parameters of glucose control were significantly lower in dogs with good control, considerable overlap existed between the 2 groups for all. All blood glucose measurements, fructosamine and GHb were consistent with good glycemic control in 60% of dogs judged to have good clinical control or with poor control in only 39% of judged to have poor clinical control dogs. The initial fasting blood glucose was 100-300 mg/dl in 80% of dogs with good clinical control and in 21% of dogs with poor clinical control. The study’s authors concluded that history, physical examination and body weight are sufficient for initial assessment of glycemic control and a glucose curve may not be necessary in a dog with apparent good clinical control when the initial morning blood glucose is 100-300 mg/dl.

Certainly, the importance of home monitoring of clinical signs cannot be over-emphasized. However, this author has some concerns with study methodology and conclusions and believes that glucose curves should be performed periodically in all diabetic patients. For aggressive animals or those who experience stress hyperglycemia in the hospital, the curves are most appropriately performed at home.

References available from author upon request.