CONTINUOUS GLUCOSE MONITORING IN DOGS AND CATS

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PATHOPHYSIOLOGY OF DIABETES MELLITUS

Diabetes mellitus (DM) is a common endocrine disease in dogs and cats which is characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize glucose, amino acids, fatty acids, and electrolytes. Insulin deficiency results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism.

Two types of DM are recognized in dogs and cats. Type I DM is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to β-cell secretagogues such as glucagon and is the most common form of DM in dogs. Type II DM is characterized by an abnormal pattern of insulin secretion in combination with peripheral insulin resistance and is the most common type of DM in cats. Type II diabetic cats may go into diabetic remission if they achieve good glycemic control however unfortunately there is no practical diagnostic test that can be used to distinguish between the two types of DM in cats. Factors that likely influence whether a diabetic cat goes into remission include the severity of pancreatic pathology, whether there is concurrent disease that causes insulin resistance, whether the cat is overweight, and whether the cat is fed a low carbohydrate diet.

DIAGNOSIS

The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss), and documentation of hyperglycemia and glycosuria. In cats, the diagnosis is complicated by stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document persistent hyperglycemia and glucosuria, but also to rule out other diseases that may cause similar clinical signs such as hyperthyroidism and gastrointestinal disease. Measurement of fructosamine concentrations or urine glucose concentrations of samples collected in the home environment, allows the clinician to distinguish between stress induced hyperglycemia, and persistent hyperglycemia due to diabetes mellitus. Measurement of fructosamine is unreliable for cats with concurrent hyperthyroidism because increased protein turnover decreases fructosamine concentration. Glucosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and post-obstructive diuresis so is not on its own diagnostic for diabetes mellitus. The presence of significant ketonuria or ketonemia and concurrent hyperglycemia is diagnostic for diabetes mellitus.

TREATMENT OF DIABETIC PATIENTS

Treatment of diabetes mellitus in dogs and cats relies on insulin therapy, dietary modification, management of concurrent illness and weight management.

INSULIN THERAPY

Table 1: Insulin products currently available commercially and used in cats and dogs in USA

Short duration:
Regular insulin (Zinc insulin crystals)
Products: Humulin R [Lilly], **Novolin R** [NovoNordisk] Both human recombinant.100 U/ml

Moderate duration:
NPH insulin (neutral protamine hagedorn)
Products: (**Humulin N** [Lilly] ,**Novolin N** [NovoNordisk] Both human recombinant 100 U/ml
Lente insulin (65% crystalline and 35% amorphous)
Product Vetsulin (Merck) pork 40 U/ml

Long duration:
PZI insulin
Insulin complexed with protamine and zinc.
Product: ProZinc [Boehringer Ingelheim] human recombinant (40 U/ml)
Glargine
Insulin analogue
Product: **Lantus [**Sanofi-Aventis], human recombinant (100 U/ml)
Detemir
Insulin analogue
Product: Levemir [NovoNordisk], human recombinant (100 U/ml)

Insulin treatment in cats: There are three insulin products that are appropriate for first line treatment of diabetes mellitus in cats; Protamine zinc insulin, Lente insulin, and Glargine insulin. NPH insulin tends to have a very short duration of action in cats and is not recommended as first line insulin.
The starting dose for insulin in a new feline diabetic patient is 1-3 U/cat (0.25 – 0.5 Unit/kg). It is recommended that insulintreatment is started at the lower end of this dose. It is difficult to predict in advance which cats will do better with which insulin formulation. Cats should be carefully monitored for occurrence of hypoglycemia, because of the possibility of remission of diabetes mellitus. A blood glucose curve should be performed 7-14 days after making any change in insulin formulation. Whichever formulation is chosen, twice a day insulin therapy is more likely to result in good glycemic control than once a day therapy. If twice a day treatment is not possible once a day therapy with PZI or Glargine can result in effective control of clinical signs in some cats.
Insulin treatment in dogs:
The most effective insulin formulations in dogs are Lente Insulin (Vetsulin/Caninsulin) and human recombinant NPH (Humulin N) at a starting dose of 0.25 - 0.5 U/kg twice a day. Use of human recombinant insulin or pure pork insulin avoids the complications that can occur due to development of anti-insulin antibodies in dogs treated with beef/pork insulin. The long acting insulin PZI has also been approved for once a day use in dogs. The starting dose for PZI is 0.7 U/kg q 24 hours. In dogs with rapid

metabolism of insulin PZI can also be administered twice a day. Insulin analogs such as Glargine and Detemir are not appropriate for initial management of canine diabetic patients, however treatment with these products may be helpful in dogs that have a very short duration of insulin action. Detemir has been evaluated in a small number of diabetic dogs. It is important to be aware that this insulin is much more potent than other insulins in the dog and the starting dose is lower. The dose needed for good glycemic control in one study ranged from 0.05-0.34 U/Kg.

Goals of insulin treatment: The primary goal of insulin therapy in diabetic patients is to control clinical signs of DM while avoiding hypoglycemia. Severe hypoglycemia can be life-threatening and even mild insulin- induced hypoglycemia can result in clinical signs of poor glycemic control due to the insulin resistance that results from secretion of anti-insulin hormones such as glucagon, growth hormone, cortisol, and epinephrine. Persistent severe hypoglycemia can lead to permanent neurologic damage. The long-term benefits of tight glycemic control, while well established in human diabetic patients have not been demonstrated in dogs and cats; although theoretically better glycemic control should result in fewer diabetic complications such recurrent infection, proteinuria, and cataract formation. The likelihood of diabetic remission in cats is higher with tighter glycemic control. The goals of diabetic regulation should therefore take into account the lifestyle of the owner, the presence of concurrent illness, the age of the patient, and the practicality of tight glucose monitoring.
Ideally the blood glucose should be maintained between 80 and 200 mg/dl, however most patients will have some blood glucose concentrations that fall above this range and most patients are clinically well regulated if most of the blood glucose concentrations are less than 300 mg/dl. Occult hypoglycemia is an important cause of poor glycemic control and can lead to unnecessary visits to the emergency clinic. If the blood glucose falls below 80 mg/dl on the BG curve, the insulin dose should be decreased. It is important to remember that it is difficult to assess the duration of insulin action if the glucose nadir is in the hypoglycemic range because this can lead to release of counter-regulatory hormones such as glucagon which drives the blood glucose back up prematurely.

MONITORING DIABETIC PATIENTS
The ideal monitoring strategy should be multimodal and individualized for the patient and owner(s). Parameters that can aid in assessing the adequacy of diabetic control include clinical signs, bodyweight, serial blood glucose concentrations measured at home or in the clinic, fructosamine concentrations, glycosylated hemoglobin concentration (HbAIC), and urine glucose concentrations. The presence of ketones in the blood or urine can also be useful to indicate the presence of impending diabetic ketoacidosis. The most important factor in assessing diabetic control is whether clinical signs are well controlled. Blood glucose concentrations, urine glucose concentrations and glycated proteins should be interpreted in the light of the clinical signs. Monitoring should be individualized to meet the needs of the patient and owner.
Blood glucose curves:
Although blood glucose curves have long been considered to be the gold standard for evaluating glycemic control, they have significant limitations, in particular the effect of

stress, and the presence of day-to-day variability. Blood glucose curves are expensive and require collection of multiple blood samples which can be stressful to the patient even when performed by the owner at home. Misinterpretation of blood glucose curves can lead to incorrect treatment decisions.

Glycosylated proteins: Measurement of glycosylated proteins allow assessment of longer-term glycemic control and can aid in interpretation of blood glucose curves. Glucose binds irreversibly to serum proteins and hemoglobin and these products persist for the life of the proteins. The resultant products can be measured in serum or whole blood respectively. Fructosamine indicates adequacy of glycemic control over the previous 2-3 weeks, while HbA1C reflects glycemic control for the previous 4-6 weeks.

Urine glucose: Urine glucose concentrations can also be used to assess glycemic control and are particularly helpful in cats to assess for the presence of diabetic remission as well as to detect relapse. Urine glucose should not be used to determine the daily dose of insulin but trends in urine glucose can be very helpful in assessing diabetic control especially if assessed on a consistent basis and recorded in a diary or log.

Continuous glucose monitoring (CGM): Newer continuous interstitial glucose monitoring (CGM) techniques are changing the approach to blood glucose monitoring. These systems allow continuous evaluation of interstitial blood glucose concentration for up to 14 days via a small flexible subcutaneous catheter, replacing the blood glucose curve. The newer systems are affordable, easy to use, and well tolerated by patients. The reports that are generated can be downloaded as a pdf or uploaded to a website and allow an integrated analysis of changes in blood glucose over a 14 day period.

The Freestyle Libre device is the most common CGM used in veterinary medicine. Purchase of the sensor and reader requires a prescription. The sensor is a one-time use disposable device while the reader is a onetime purchase and can be used multiple times with different sensors. The reader allows wireless monitoring of the interstitial glucose. Alternatively, you can download the Freestyle Libre app for Android or iPhone and download the data to your phone from the sensor. The reader and the app can be used together as long as the reader is initially used to set up the sensor.

Two different devices are available: the Libre 14 day device and the Freestyle Libre 2 device. The Freestyle Libre 14 day is the device most frequently used in cats and dogs. A video demonstrating how to place a freestyle Libre 14 day sensor can be accessed using the QR code below.

Depending upon the patient, the sensor can be left uncovered, or can be protected by an adherent patch or dressing, a pet sweater, or a thunder shirt. A covering is

recommended in active patients or patients with house mates that might attempt to remove the sensor. The reader is able to read the sensor through a jacket or bandage. Although the sensor is waterproof, we do not recommend bathing the pet or allowing the pet to swim while the sensor is in place.

The Freestyle Libre sensor (FSL) measures the interstitial glucose every minute and stores this data every 15 minutes on the sensor disc. This disc can store up to 8 hours of data. Every time the sensor is scanned, the data is downloaded onto the reader. The sensor can be scanned at any time but it needs to be scanned at least once every 8 hours in order to obtain continuous readings. Data from the reader can be uploaded to a computer for viewing as a pdf file any time during the life of the sensor. Complications with both the device and the patient do sometimes occur. Patients can develop erythema at the placement site and occasionally abscesses at the insertion site develop.

The FSL generates 24 hour interstitial glucose curves for up to 14 days, although early detachment occurs in as many as 60-80% of dogs and cats. The FSL can measure glucose concentrations between 40 and 500 mg/dl, however the graphs that are generated in the FSL reports do not display glucose concentrations greater than 350 mg/dl. The FSL is an important tool in patients with diabetic ketoacidosis, in patients with newly diagnosed DM and in unstable diabetic patients, in which it can be used continuously until better glycemic control is achieved. The FSL is also very useful for routine intermittent monitoring of glycemic control in stable patients.
Interstitial glucose measured by the FSL, correlates well with both peripheral blood glucose measured by both point of care glucometers, and blood glucose measured by reference methods. Although overall there is a good correlation, the FSL usually slightly overestimates the blood glucose in the euglycemic and hyperglycemic ranges, while slightly underestimating the blood glucose in the hypoglycemic range. It is important to understand that there is a lag of a few minutes between changes in the blood glucose and changes in the interstitial glucose, so these measurements may differ, especially when the blood glucose is changing quickly. When a consensus error grid method was used to analyze the performance of the FSL compared to a reference method, the difference between the two measurements had little or no effect on clinical decision making for more than 98% of the samples. The performance of the FSL device is not affected by ketosis, but it is slightly less accurate in dehydrated animals. This should be taken into account when using the FSL in patients with Diabetic ketoacidosis.
The data from the FSL, can be viewed in real time using either the FSL reader or a cell phone app. Data from the FSL reader can be uploaded to a computer using free software, or can be uploaded to the Libreview website. The Libreview website allows the data from multiple patients to be stored in the cloud, and accessed not only by the owner, but also by all the veterinary care providers in a practice. Data from the Librelink cell phone app can also be wirelessly uploaded to the Libreview website. Once the data is uploaded, the user can generate a summary report, which can be viewed on- line or downloaded as a pdf.
The FSL summary report has a number of different viewing options that display the 24 hour interstitial glucose either in a day- by- day format or an integrated format. The

integrated format allows an assessment of daily trends in interstitial glucose while the day-by-day format allows better assessment of day to day variability.
A major advantage of the FSL is the ability to collect 24-hour data for a diabetic patient. This is very helpful for determining different insulin requirements between the daytime and nighttime hours as well as to evaluate response to long-acting insulins given once a day. The other important advantage of the FSL curves is the ability to evaluate day-to-day variability in insulin response.
Interpretation of individual curves is similar to interpretation of a traditional blood glucose curve but with the ability to better appreciate day-to-day variability. The glucose nadir, duration of insulin effect and average glucose can be easily determined. Ideally, the glucose nadir should fall between 80 and 150 mg/dl and the glucose concentration should be below 300 mg/dl for the majority of the day. Problems that can be detected using the FSL glucose reports include inadequate dose of insulin, inadequate duration of insulin action (rapid metabolism), insulin-induced hypoglycemia and lack of response to insulin. Lack of response to insulin suggests either poor client compliance or insulin resistance. Based on the assessment of the curve, a change in insulin dose or formulation can then be made and the response assessed while the sensor is still in place. Because the glucose measurements are available in real time, clinically relevant hypoglycemia can be diagnosed and treated immediately, and the insulin dose decreased. When using the FSL to adjust the insulin dose, it is still important to wait 5-7 days between dose increases. With a sensor life of 14 days, it is usually possible to make two adjustments to the insulin dose during the life of the sensor; of course, the dose can be decreased multiple times if necessary.
Although the correlation between the FSL and point of care (POC) glucometers is usually good, sensor failure or sensor errors can and do occur. If the FSL glucose measurements do not fit with the clinical picture, the blood glucose measurement should be measured using a POC glucometer or another trusted method. Indications of sensor failure include an error message, a message indicating that the sensor should be scanned again at a later time, gaps in data, and unexpectedly wide swings in the blood glucose that do not fit with clinical signs. In these situations, if the results of the FSL do not correlate with the measurement from the POC device, the FSL sensor should be replaced.
In summary the FSL is a device that can be very valuable in assessment of glycemic control in dogs and cats. Having a good understanding of this technology allows maximum utilization of the advantages of this monitoring system and can improve the ability to accurately monitor diabetic patients.

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