UNCONTROLLED CANINE DIABETES

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Ian Battersby and Patricia Ibarrola discuss monitoring methodologies and the causal links behind instability, and suggest protocols for dealing with this condition

AS veterinarians, our goal is to resolve the clinical signs associated with diabetes mellitus (PU/PD, polyphagia and weight loss) and to minimise complications such as hypoglycaemia, diabetic ketoacidosis and urinary tract infections.

The final objective is to achieve these aims in a manner that fits the owner's lifestyle. Poor control is when these goals are not achieved.

Whether a dog is a newly diagnosed diabetic and difficult to stabilise, or suddenly becomes unstable after a period of successful therapy, the diagnostic approach is similar.

Regardless of the presentation, before embarking on investigations to determine the cause of the instability, a good understanding of the factors that influence insulin therapy is essential so that investigations can be performed in a logical manner.

This article will review the methods of monitoring our diabetic patients and the causes of instability (Figure 1), before outlining a broad approach for these cases.

Clinical manifestations of poor control

Excessive insulin therapy can result in hypoglycaemia, causing weakness and seizures that can be life threatening.

Relative or absolute insulin deficiency leads to persistent hyperglycaemia, weight loss, PU/ PD and an increased risk of infection (skin or urinary tract).

This poor control can speed the onset of cataracts and lensinduced uveitis.

If untreated, insulin deficiency leads to increased lipolysis, which increases the availability of free fatty acids to the liver, promoting ketogenesis.

Ketosis can progress to ketoacidosis, which can lead to anorexia, vomiting, collapse, seizures and death.

Monitoring treatment efficacy

A variety of different methods to assess the stability of diabetic dogs are available. These measures can be done alone or in combination, and include blood tests (such as fructosamine concentrations), blood glucose curves and urine glucose measurements. However, the value of information – such as the daily water intake and trends in bodyweight – cannot be underestimated.

Water intake and bodyweight

Daily water intake and weekly bodyweight measurements offer simple, but invaluable, information. A well-controlled diabetic will have a relatively stable water intake and weight. If insulin therapy is insufficient, then weight loss will occur and water intake will increase. As the treatment of diabetes mellitus in veterinary patients revolves around a consistent routine, there can be some slight day-to-day variation in water intake and the odd day where water intake may be unexpectedly high. This reflects the fact that it is impossible to ensure that the daily routine will be the same every day. Concern should only be raised if the increase in water intake persists.

Clinical history

Signs of exercise intolerance, weakness or collapse would raise concerns of excessive insulin therapy, resulting in hypoglycaemia.

Urine glucose measurements

Urine glucose measurement is a traditional method for assessing diabetic stability.

To maximise the interpretation of this method, an understanding of the limitations of urine glucose testing is needed. Firstly, the reading reflects blood glucose over the time since the last urination, during which the glucose may have been very low but also high – the urine reading will only reflect the period of hyperglycaemia. Secondly, to obtain a positive urine glucose measurement, blood

glucose must be over the renal threshold (approximately 12mmol/L).

A negative result would, therefore, reflect a period in which the blood glucose was below this level. It would not, however, differentiate between a mild hyperglycaemia, normoglycaemia or hypoglycaemia. The authors do not use urine glucose measurements to assess the stability of a diabetic or to adjust insulin therapy, due to the limitations of interpretation. However, the authors do provide owners with reagent strips, which can be used to aid early ketosis detection when there is concern.

Glycosylated proteins

Blood levels of glycosylated proteins reflect glycaemic control over a period of time preceding sampling (glycosylated haemoglobin, two to three months; fructosamine, two weeks; glycosylated albumin, two to three weeks).

A well-controlled diabetic should have glycosylated protein levels just above the normal reference range. A normal fructosamine level (particularly low normal) in a patient receiving insulin therapy should raise concerns of excessive therapy. These patients are likely to be close to, or have developed periods of, asymptomatic hypoglycaemia. In addition, well-controlled patients occasionally present with discordant fructosamine results, where despite good glycaemic control based on glucose curves (Figure 2) and clinical signs, fructosamine levels remain high. When interpreting the results of glycosylated proteins, it should be remembered that the results reflect trends of glycaemic control over a period of weeks and months, meaning regular short periods of hypoglycaemia will not be reflected in the result. A recent persistent hyperglycaemia may also not be reflected in the results.

Blood glucose curves

When performing a glucose curve we are trying to determine the following information.

• Is insulin effective at lowering blood glucose?

• What is the glucose nadir?

• What is the duration of insulin action?

When performing a glucose curve, it is important to maintain the same daily routine.

Stress can influence glucose levels, so every attempt should be made to minimise patient stress – for example, the authors hospitalise the patient the night before to familiarise them with the environment.

If you commit to performing a glucose curve for diagnostic purposes, then every effort should be made to maximise the information you can obtain. Common mistakes are not sampling frequently enough and not performing the curve for a sufficient time period.

As a minimum, samples should be taken every two hours; however, even at this interval, a Somogyi overswing can be missed.

The authors prefer to measure blood glucose hourly (when possible), particularly in patients in which an overswing is considered a possibility. Sampling should also continue until the duration of the insulin activity is established.

Continuous interstitial glucose monitoring devices

Devices are available that measure interstitial glucose levels via an electrode placed subcutaneously. Following calibration, the readings the devices provide are able to produce blood glucose curves. Once the electrode is inserted, a transmitter (white disc; Figures 3a to 3d) is attached. The measurements are then transmitted to a reader that remains within three metres of the patient during the test. To calibrate the devices, a blood sample is required every six to eight hours, and the information is entered into a reader. One limitation of the devices that are currently available is that patients must have a period in which blood glucose is below 22mmol/L for the device to establish a curve.

Home blood glucose testing

The owners, under the guidance of a veterinarian, are taught to take pinprick samples from the patient's ear or pad. Kits containing all the equipment needed (a glucometer, sampling lance and replacement needles for the lances) and demonstration videos for the owner are now available. The obvious advantage of home testing is that the owner is able to maintain a consistent routine and minimise any stress that may develop with hospitalisation. However, not all owners will be comfortable with this procedure.

Causes of poor control

• Daily routine

Standard management in veterinary species revolves around consistency of the daily routine combined with one or two injections of a sustained release insulin preparation. Important components of the routine include a consistent relationship between meal times and injections, consistent food types and set exercise times.

• Insulin delivery

– **Storage** – preparations are normally refrigerated (try to avoid freezing and extreme temperatures).

– **Accurate dosing** – rolling to prevent bubble formation.

– **Injection technique** – consider this method in a diabetic dog that is initially difficult to stabilise. In a patient that becomes unstable after responding well to treatment, ensure that the person responsible for injecting has not changed. It is also more consistent if only one person performs the injections.

– **Absorption** – poor absorption is not common in dogs when using lente and protamine zinc insulin (PZI) preparations. Occasionally, patients develop thickening of the skin with repeated injections in the same site.

Insulin activity

General guidelines on different preparations' duration of activity are available in texts, such as the BSAVA formulary. This information is useful when starting treatment, but is only a guide as every patient will have its own individual response to the insulin prescribed.

Duration

In most dogs, the duration of action of lente insulins lends itself to a twice-a-day regime.

• **Prolonged duration** – when duration of action is longer than 12 hours, twice-daily injections may lead to an overlap in insulin activity and a subsequent piggybacking of doses. This results in a higher dose being given due to residual insulin activity from the last injection. Hypoglycaemia and/or the Somogyi phenomenon can occur. If insulin activity is longer than 16 hours, then switching to a longer-acting preparation once a day is suggested. If insulin activity is less then 16 hours, but greater than 12 hours, continue with a twice-aday regime, but with a shorteracting preparation.

• **Short duration** – owners may comment on intermittent activity. Questioning may reveal that PU/PD occurs a few hours prior to the next injection. This can be misinterpreted as underdosing (based on clinical signs or urine glucose measurements) and the dose is increased inappropriately, which can result in a Somogyi phenomenon (Figure 4). If the duration of action is found to be too short when based on a glucose curve, the options are to increase the frequency of injections or to switch to a longer-acting preparation.

Dosage

• **Underdosage** – most dogs can be stabilised with 0.5IU/kg to 1.0IU/kg of lente insulin bid. If insulin underdosage is suspected, then increase in small increments (one to five units per injection, depending on the size of dog). After each adjustment, allow three to four days before reassessing the response to treatment.

• **Relative underdosage/insulin resistance** – when a patient is receiving 1.5IU/kg to 2IU/kg of insulin with minimal effect on serum glucose, insulin resistance should be suspected. This could reflect co-existing disease or Somogyi phenomenon.

Overdosage and Somogyi overswing

Insulin overdosage leads to hypoglycaemia, which may be asymptomatic, symptomatic (seizures) or lead to the Somogyi phenomenon. If the hypoglycaemia is asymptomatic, insulin dose is normally reduced by 10 to 20 per cent. In the case of symptomatic hypoglycaemia, insulin therapy should be stopped and emergency treatment given. The reintroduction of insulin at a significantly lower dose (30 to 40 per cent) should be withheld until hyperglycaemia returns.

The Somogyi phenomenon reflects the body's protective mechanisms to prevent hypoglycaemia if blood glucose falls below 3.5mmol/L or rapidly decreases. Hypoglycaemia induces hepatic glycogenolysis and diabetogenic hormones, such as adrenaline and glucagon, are released, which leads to hyperglycaemia. This hyperglycaemia cannot be controlled. The clinical signs are usually predominated by hyperglycaemia, rather than signs of weakness (hypoglycaemia), and can be misinterpreted as an insulin under-dosage.

The most challenging aspect of the Somogyi overswing reflects the duration of action of the diabetogenic hormones, which can induce insulin resistance for a prolonged period (24 to 72 hours; Figure 5). Therefore, a curve taken 24 hours after an episode of hypoglycaemia may give the impression of insulin resistance or underdosage.

Due to the individual responses to insulin, Somogyi overswing should be ruled out in all unstable patients, regardless of the insulin dosage used.

Anti-insulin antibodies

Anti-insulin antibodies can enhance the duration of insulin action (by acting as a carrier) or shorten duration of action by neutralisation. Conversely, antibodies may have no effect on glycaemic control. The most commonly observed effect is reduced effectiveness of insulin, resulting in erratic fluctuations in blood glucose levels.

Anti-insulin antibodies affecting glycaemic control are uncommon, but should be considered in patients when other factors have been excluded.

Concurrent disease

Concurrent disease can affect a patient's initial response to insulin, or change insulin requirements in a previously stable patient.

Mechanisms that can play a role include increased insulin degradation, altered receptor binding or the production of insulin antagonising hormones.

Insulin resistance should be considered when dosages of 2IU/kg are required but suspicions should be raised at 1.5IU/ kg. Examples of concurrent issues include:

• infection – especially urinary tract infection;

• inflammatory or immune-mediated;

• endocrine – hypothyroidism, hyperadrenocorticism, diestrus, pheochromocytoma and glucagonoma;

• pancreatic – pancreatitis and/or exocrine pancreatic insufficiency;

• neoplasia;

• drugs – interactions (such as ACE inhibitors or beta blockers) may increase the hypoglycaemic effects of insulin – for example, prednisolone causes insulin resistance;

• obesity – induces a down regulation of insulin receptors, reduces insulin binding and affects glucose metabolism (weight loss can improve tissue responsiveness to insulin); and

• others – hyperlipidaemia, renal, cardiac and liver insufficiency.

Diagnostic approach

• Review the clinical history and perform a thorough physical examination. In a newly diagnosed entire bitch, diestrus should be considered regardless of observed seasons. Progesterone measurements should be considered.

• Review insulin storage, injection technique and so on.

• Review consistency of routine, such as feeding times, diet and daily activities.

• Perform urinalysis – including sediment and culture – and check for ketones.

• Complete blood count/ biochemistry – diabetes mellitus can increase cholesterol and cause mild increases in alanine aminotransferase/alkaline phosphatase.

• Glucose curve (hourly at least until next insulin injection) – assess duration, peak and trough glucose levels and beware of the persistent effects of the Somogyi phenomenon. Further testing based on findings up to this point include:

• thoracic radiographs;

• abdominal ultrasound – particularly the pancreas;

• pancreatitis, testing pancreatic lipase immunoreactivity/trypsin-like immunoreactivity;

• endocrine testing – T4/thyroid-stimulating hormone, adrenocorticotropic hormone stimulation test, low-dose dexamethasone suppression test – all these tests can be affected by concurrent illness and metabolic stress seen in an unstable diabetic;

• blood pressure; and

• anti-insulin antibodies and/or therapeutic trial with different insulin.