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Veterinary Technical Guidelines

for the successful management of the diabetic dog and cat

MSD Animal Health

Foreword

Diabetes is a complex and dynamic disease, with many factors contributing to successful management. These Veterinary Technical Guidelines have been updated in collaboration with Dr Linda Fleeman.

Dr Linda Fleeman runs Animal Diabetes Australia, a clinical service for diabetic dogs and cats. She is an internationally renowned expert on canine and feline diabetes and has published numerous papers on the clinical management of diabetes in dogs and cats. Dr Fleeman graduated from the University of Queensland and completed a Small Animal Medicine Internship at Murdoch University and a Residency in Small Animal Medicine at the University of Melbourne. This was followed by a PhD at the University of Queensland on the clinical management of diabetes mellitus in dogs. She held positions as Lecturer in Small Animal Medicine at the University of Queensland and Senior Lecturer in Small Animal Medicine at the University of Sydney, before deciding to return to private clinical practice in January 2010.

Disclaimer: These guidelines are intended to provide general advice about the use of Caninsulin for the treatment of diabetes mellitus in dogs and cats, based on best practice concepts and published scientific data. All clinical decisions for the treatment of any diabetic patient remain the responsibility of the prescribing veterinarian.

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Incidence and aetiology

Introduction

Diabetes mellitus is a common endocrine disorder of dogs and cats which results from an absolute or relative insulin deficiency. In general, the prognosis is good, provided that the animal receives adequate treatment to control the clinical signs.

Insulin treatment is the cornerstone of successful management, but appropriate diet, exercise and a regular lifestyle are also important considerations (Fig.1).

First-rate communication between the pet owner and the veterinarian is of major importance. Your attitude to diabetes mellitus will largely determine the owner's motivation and compliance with treatment.

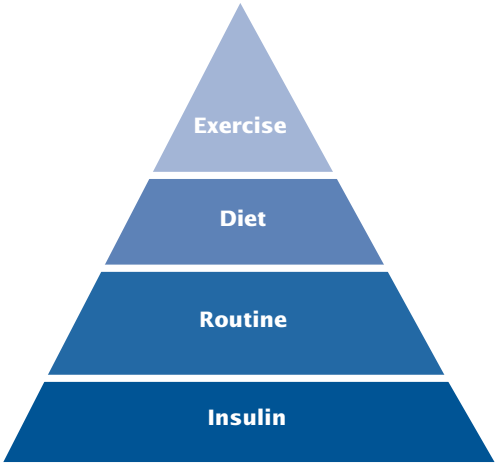


Figure 1: Factors influencing successful diabetes management.

Incidence

The incidence of diabetes mellitus in dogs and cats is estimated to be around 1:400[1]. Diabetes mellitus occurs most commonly in middle-aged and older dogs and cats. Mixed breed dogs and cats are more commonly affected, but some pure breeds are over-represented. Breed predisposition varies with geographic region, with the Australian situation most closely matching that of the UK, where over-represented dog breeds include Miniature Schnauzers, Samoyeds, Terrier breeds, and Labrador Retrievers[2]. In Australia, Maltese and Rottweilers are also frequently affected. Entire bitches are at increased risk, especially if they are also overweight. An Australian study observed a disease prevalence of 22.4 cats per 1000 amongst the Burmese breed, compared with a disease incidence of 7.6 cats per 1000 in domestic short- and long-haired breeds[3].

Aetiology

Diabetes mellitus can originate from either pancreatic or non-pancreatic disease.

Diabetes mellitus due to pancreatic disease

Endocrine

Destruction of endocrine pancreatic tissue can lead to diabetes mellitus. In dogs, there is some evidence that autoimmune destruction of the islets of Langerhans plays a role in the pathogenesis of diabetes. In cats, amyloid deposition may contribute to the destruction of the islets of Langerhans.

Exocrine

Severe inflammation or neoplasia of the exocrine pancreas can also lead to loss of islet function. In dogs, chronic pancreatitis causes loss of both endocrine and exocrine pancreatic tissue[4]. In these cases, diabetes might be complicated by exocrine pancreatic insufficiency.

Diabetes mellitus due to disease not primarily of pancreatic origin

Overproduction of counteracting hormones and insulin resistance

Growth hormone excess

Progesterone-induced

In dogs, progesterone produced during the luteal phase induces the production of growth hormone by the mammary gland, which counteracts the action of insulin[5].

Pituitary origin – acromegaly

Acromegaly (hypersomatotropism) is caused by growth hormone excess. This is predominately caused by a pituitary adenoma in cats[6].

Corticosteroids

Corticosteroids stimulate gluconeogenesis, and thus cause insulin resistance - the failure of cells to respond to the normal actions of insulin. Most dogs do not develop diabetes mellitus with chronic corticosteroid therapy or spontaneous hyperadrenocorticism alone. For overt diabetes to develop, underlying reduced beta cell function resulting from immunological processes or pancreatitis may be required.

Progestagens

The use of exogenous progestagens can lead to growth hormone excess. Progestagens also have an affinity for glucocorticoid receptors.

Obesity

Obesity causes insulin resistance and so increases the risk of the forms of diabetes associated with insulin resistance, such as occurs in cats and intact female dogs.

Pathogenesis and clinical signs

Pathogenesis

Diabetes mellitus is a paradox: simultaneous extracellular hyperglycaemia and intracellular glucose deficiency. The consequences of this paradox are shown in Figs. 2 and 3[5].

Figure 2: Extracellular hyperglycaemia

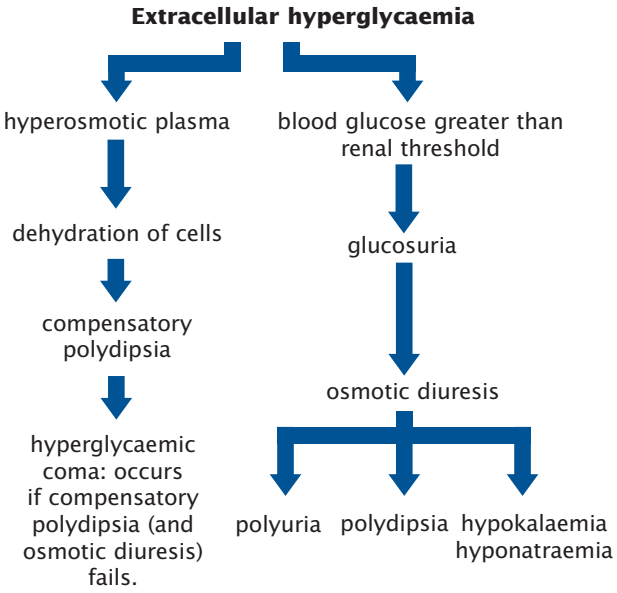
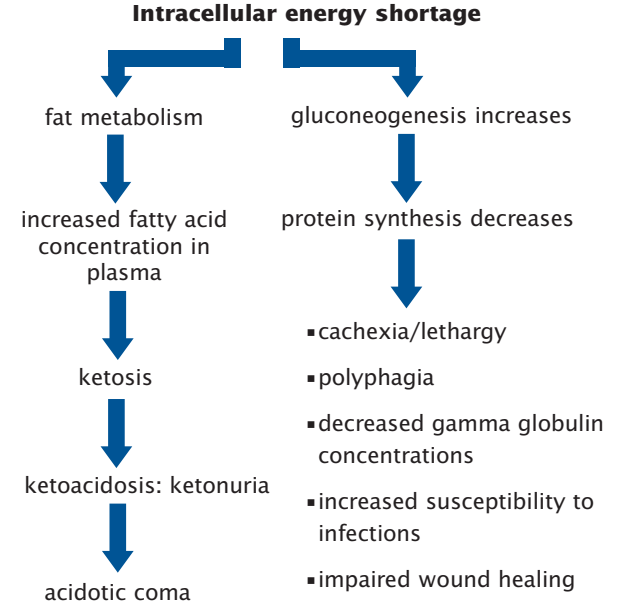


Figure 3: Intracellular energy shortage



Clinical signs

There are two clinical scenarios in diabetes mellitus:

1. Uncomplicated;
2. Complicated by ketoacidosis.

Uncomplicated diabetes mellitus

The classical signs are:

- *Polyuria and polydipsia*
- *Cachexia*
- *Polyphagia*
- *Increased susceptibility to infections (e.g. urinary tract infections)*

Complications include:

- *Cataracts (mainly in dogs)*
- *Peripheral neuropathy (mainly in cats)*

Complicated by dehydration, ketoacidosis, and/or hyperosmolarity

The importance of the compensatory role of polydipsia and polyphagia in the pathophysiology of diabetes becomes apparent when these compensatory mechanisms fail. Any concurrent illness in diabetic patients that causes inappetence or anorexia and vomiting is rapidly complicated by dehydration, depression, and ketosis. The majority of diabetic dogs and cats that present with diabetic ketoacidosis have at least one concurrent disease, with acute pancreatitis the most common diagnosis in dogs[7], and liver disease and pancreatitis the most common concurrent conditions reported in cats[8].

Diagnosis and management

Diagnosis

Diabetes mellitus is not the only cause of polyuria, polydipsia and weight loss. A preliminary diagnosis of diabetes mellitus based on clinical signs must be confirmed by urine and blood testing.

Reference intervals for blood glucose concentration in non-diabetic, healthy animals are approximately 3.5 - 6.1 mmol/L in dogs and 2.6 - 8.4 mmol/L in cats. The renal threshold is around 10 - 14 mmol/L, but there is individual variation. If the blood glucose concentration exceeds this threshold, glucose is excreted in the urine (glucosuria).

Transient hyperglycaemia can occur particularly in cats in stress situations, usually where struggling is involved. Fructosamine concentrations are correlated with the average blood glucose concentration over the previous 1- 2 weeks. Fructosamine measurement may be a useful tool in confirming a diagnosis of diabetes mellitus, particularly in cats.

Management

General considerations

Diabetes is one of the few conditions affecting dogs and cats that requires owners to do almost all of the treatment, and so it is inevitable that a diagnosis of diabetes will have some impact on the owner's lifestyle. It is crucial therefore that we manage the owner's expectations and concerns as well as the pet's needs. Failure to do so might result in euthanasia of the animal. Treatment of diabetes mellitus is likely to succeed only if the pet owner understands all aspects of its management, including the importance of diet and establishment of a daily treatment routine. Investment of time in a careful explanation of all aspects of diabetes management is strongly recommended. A flexible approach that considers both owner and pet needs will allow appropriate individualisation in each case.

Spaying

If diabetes mellitus has been diagnosed in an entire bitch, insulin treatment and immediate spaying (ovariohysterectomy) should be considered to prevent further exposure to endogenous progesterone. Remission of the diabetes will occur in approximately 10% of cases[19].

Following surgery, regular monitoring is therefore necessary until the animal's condition is stable.

Remission typically occurs within a few days. In those that do not achieve remission, the response to insulin will often improve and the insulin demand will decrease accordingly.

Diabetes management with Caninsulin

Caninsulin is an aqueous suspension of 40 International Units (IU) per mL of highly purified porcine insulin, consisting of approximately 35% amorphous and 65% crystalline zinc insulin. Caninsulin is available in vials and cartridges and is administered using a U-40 insulin syringe or VetPen. Due to differences in metabolism, the duration of activity and other pharmacokinetic parameters of any particular insulin product will vary from animal to animal.

Pharmacokinetics of Caninsulin

In dogs the amorphous fraction has peak activity approximately 3 hours after subcutaneous administration, and its effect lasts for about 8 hours. This effect is maintained by the crystalline fraction, which has a slower onset of action and peak effect from 8 to 14 hours following injection[9,10]. The total duration of effect ranges from 14 to 24 hours depending on the individual dog. The duration of activity of Caninsulin may be sufficient to treat dogs once-daily. However, in most cases, injections have to be given twice-daily.

In cats, the maximum effect is seen around 4 hours after administration and the total duration of action is 12 hours[11]. The duration of action of Caninsulin is shorter in cats than in dogs, and as a result, all cats require twice-daily injections. Twice-daily injection of Caninsulin can provide sufficiently good glycaemic control that can result in remission of the clinical signs[11].

It important to ensure the amorphous and crystalline fractions of Caninsulin are well mixed prior to administration.

Caninsulin 2.5mL & 10mL vials

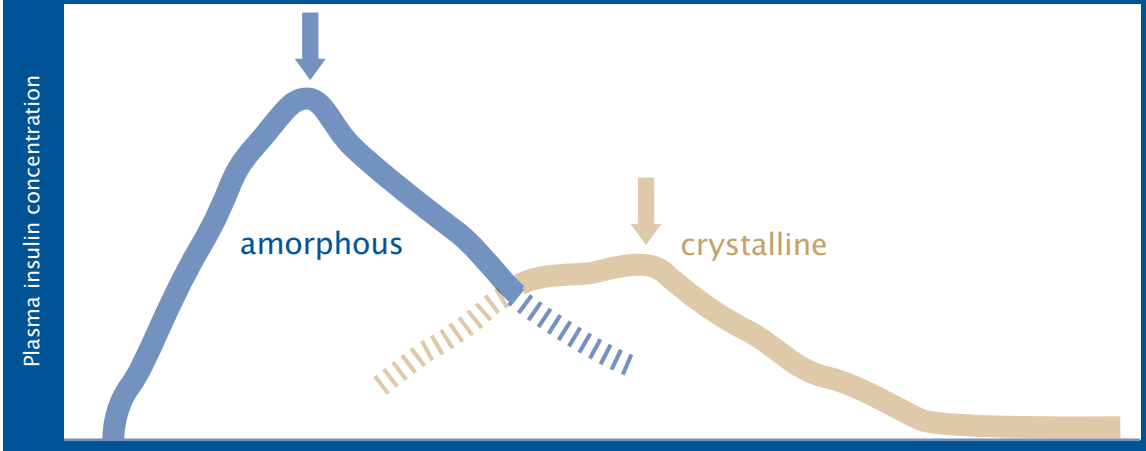
Shake the vial thoroughly until a homogeneous, uniform milky suspension is obtained. Foam on the surface of the suspension formed during shaking should be allowed to disperse before the product is used and, if required, the product should be gently mixed to maintain a homogeneous, uniformly milky suspension before use.

Caninsulin VetPen 2.7mL cartridges

Before loading cartridges into the pens, turn Caninsulin VetPen cartridges up and down at least 10 times until the insulin appears uniformly milky. Each VetPen cartridge contains two colourless glass beads to aid resuspendability of the insulin suspension before use. Ensure that VetPen is prepared for each use in accordance with the instruction leaflet accompanying the VetPen Starter Kit. VetPen must be turned up and down at least 10 times and primed before each use.

Agglomerates can form in insulin suspensions: Do not use Caninsulin vials or cartridges if visible agglomerates persist after shaking Caninsulin vials or inverting VetPen thoroughly.

Figure 4: Schematic representation of Caninsulin concentration in dogs showing biphasic activity
(adapted from Martin *et al*, 2001)



Goals of successful Caninsulin therapy

The establishment of a therapeutic regimen at home is the first goal of managing the diabetic patient. Maintenance insulin requirements can be affected by diet, activity level, and stress. Establishment of a consistent treatment and feeding routine is an important long-term goal and owners may take 1-3 weeks to incorporate all the changes into their lifestyle, especially managing their pet's diet changes. Many owners will require considerable guidance and support during this adjustment phase. It is recommended that insulin dose adjustments are delayed until the owner's home routine is established and the animal has been successfully transitioned to the new diet and feeding regimen.

The most important goal of managing a diabetic patient is to resolve the clinical signs that are associated with the disease (i.e. polyuria, polydipsia, weight loss, lethargy and polyphagia or inappetence) **without causing clinical hypoglycaemia (i.e. neuroglycopenia).**

Adequate glycaemic control cannot be achieved in diabetic pets without regular administration of exogenous insulin. **However, aiming for normoglycaemia simply increases the risk of unexpected neuroglycopenia.** Resolution of the clinical signs will restore normal quality of life to both the patient and its owner. Well-controlled diabetic pets are active and alert, maintain optimal body condition, are not polyuric or polydipsic, and have no ketonuria.

The final goal of therapy is for our patients to enter remission where possible. This may be achieved in 30% or more of 'Type 2' diabetic cats with good glycaemic control. It is also possible in a few cases of secondary diabetes mellitus in dogs, where the primary disease causing insulin antagonism is treated, or by ovariohysterectomy of entire bitches where the diabetes is associated with dioestrus or pregnancy.

Goals of Therapy

- Establish a treatment regimen
- Eliminate clinical signs
- Minimise risk of insulin-induced neuroglycopenia
- Restore normal quality of life
- Prevent long-term disease complications
- Induce remission where possible

Cataract Formation in Dogs

Cataract formation is the most common long-term complication of diabetes in dogs. Approximately 30% of diabetic dogs will have reduced vision on initial presentation, with the majority going on to develop cataracts within 5-6 months of diagnosis. By 16 months, approximately 80% of diabetic dogs have significant cataract formation. The risk of cataract development seems to be unrelated to the level of hyperglycaemia, but increases with age[18].

Starting insulin therapy in the 'healthy' diabetic patient

The 'healthy', uncomplicated diabetic patient is defined as an animal that has clinical signs of insulin deficiency manifesting as polyuria, polydipsia, polyphagia, weight loss and/or lethargy, but is otherwise normal. Importantly, normal hydration and appetite are maintained. Ketones can be present in the blood and/or urine of 'healthy', uncomplicated diabetic patients and their presence does not necessarily indicate diabetic ketoacidosis.

In other words, this is the diabetic who is still compensating for the disease without concurrent electrolyte imbalances (e.g. acidosis), renal failure, or gastrointestinal compromise. These patients generally require little or no supportive care, and once started on their Caninsulin therapy are able to be managed as outpatients. In contrast, Caninsulin is not recommended for the initial treatment of animals presented with diabetic ketoacidosis, and intravenous fluids and alternative insulin treatment regimens should be instituted until a normal appetite returns.

Dogs

The healthy 'uncomplicated' diabetic dog is usually started on Caninsulin at 0.25 - 0.5 IU per kilogram bodyweight injected subcutaneously every 12 hours, feeding the dog half its daily food ration at the same time as each injection. Dr. Fleeman's clinical experience has shown that the higher end of the dose range (0.5 IU per kilogram) is appropriate for the majority of newly-diagnosed diabetic dogs. The lower dose of 0.25 IU per kilogram should be reserved for dogs with mild clinical signs and relatively mild hyperglycaemia.

Most diabetic dogs can be treated with twice-daily administration of Caninsulin. In some dogs, it is possible to achieve acceptable diabetic control with once-daily administration.

Trial work and experience has shown that for an intermediate-acting insulin like Caninsulin, the label-recommended dose of 0.25 - 0.5 IU per kilogram bodyweight is a safe starting dose and that most dogs ultimately stabilise better on twice-daily injections. Because the dose required with twice-daily therapy is less insulin per injection than those dogs on a single daily injection, there is reduced risk of hypoglycaemia and better glycaemic control over 24 hours by giving less insulin more often.

Cats

Cats metabolise insulin faster than dogs, therefore all cats require twice-daily Caninsulin injections.

Managing the feline diabetic patient can often be difficult and frustrating. Stress hyperglycaemia can make it difficult to interpret blood glucose measurements and often leads to inappropriate insulin dose adjustments. Stress hyperglycaemia results from both psychological stress and illness.

Ideally no more than 2 units per injection should be administered twice daily in the first 3 weeks of treatment.

In a substantial proportion of cats, diabetic remission is possible if good glycaemic control can be achieved. Remission is defined as euglycaemia and/or consistent negative glycosuria for 4 or more weeks after withdrawal of insulin therapy. It occurs most commonly after 3 - 6 months of insulin therapy and can last for months or years.

Insulin therapy in 'healthy' diabetic patients

- Action and duration of exogenous insulin is unique to each patient.
- Owner records and glucose measurements are essential for establishing an appropriate dose and frequency of administration.
- Most dogs respond better to twice-daily treatment.
- All cats require twice-daily Caninsulin administration.
- With good glycaemic control some cats will go into remission.
- Ovariohysterectomy should be strongly considered for entire female pets to permit more effective stabilisation.

Twice-daily Caninsulin regimen (dogs and cats)

All cats and most dogs should be started on Caninsulin injections every 12 hours.

The recommended starting dose of insulin is 0.25 - 0.5 IU per kilogram, every 12 hours, **rounded down to the nearest whole unit.** For obese or thin cats and dogs, estimate the pet's **ideal bodyweight to calculate the initial insulin dose.** It is very important that the diabetic patient is given their insulin injection on time. When an injection cannot be given on time it is best to miss that dose completely. Occasionally missing a single injection does not usually cause clinical problems.

Suggested protocol

The overall goal is to establish an effective and practical treatment regimen at home, hence reliance on information gathered while the animal is hospitalised should be minimised. Monitoring blood glucose concentrations in the clinic will not be reliable in all diabetic animals and alternative monitoring methods may be recommended[13].

- After diagnosis, admit the dog/cat to the hospital to begin Caninsulin therapy.
- Measure blood glucose concentration before starting insulin therapy.
  - If the blood glucose concentration is <20 mmol/L, start Caninsulin at 0.25 IU/kg bodyweight every 12 hours.
  - If the blood glucose concentration is >20 mmol/L, start Caninsulin at 0.5 IU/kg bodyweight every 12 hours.
  - For cats, ideally no more than 2 IU per injection should be administered twice-daily in the first 3 weeks of treatment.
- For dogs, the daily food ration should be divided equally into two parts. Feed half of the daily food ration with each injection. For cats, the timing of feeding is not as important, and they can follow their usual eating pattern[12]. Animals that do not reliably eat in hospital should be fed at home. Calorie restriction is not recommended at this stage and, if indicated, should not be introduced until pathological weight loss has been arrested. Similarly, any recommended diet change should be introduced only when the animal is settled in its home environment.
- On Day 1, take blood glucose measurements every 2 hours. The aim is simply to establish that the initial dose of insulin does not cause hypoglycaemia or drop the blood glucose concentration too quickly. **We are not looking for perfect control at this time.**
- The blood glucose concentration should:
  - Not drop <8 mmol/L over the entire first day AND
  - Be >15 mmol/L (cats) and be >10 mmol/L (dogs) before the next 2 consecutive doses are due.
- If there is a an excessive glucose-lowering response to the insulin, decrease the insulin dose by 10% and continue monitoring.
- The insulin dose rate at home should remain the same as at discharge for minimum 1 - 3 weeks, or until the owner has established the treatment and feeding routine at home, unless hypoglycaemia and/or diabetic remission are suspected.
- Schedule a revisit for 1 - 3 weeks' time to reassess clinical signs and perform blood glucose measurements: Refer to **'Monitoring diabetic control'** and '**Insulin dose adjustments'.**

Once-daily Caninsulin regimen (dogs only)

The initial dose for dogs starting Caninsulin with once-daily administration is 0.5 IU per kilogram bodyweight (rounded down to the nearest whole unit). For obese and thin dogs, **estimate ideal bodyweight** to calculate the initial insulin dose.

Suggested protocol

- After diagnosis, admit the dog to the hospital to begin Caninsulin therapy.
- Start Caninsulin at 0.5 IU/kg bodyweight once-daily.
- Feed one half of their daily ration just prior to the insulin injection and the remainder approximately 7.5 hours later (e.g. 8.30am and 4.00pm).
- On Day 1, take blood glucose measurements every 2 hours. The aim is simply to establish that the initial dose of insulin does not cause hypoglycaemia, or drop the blood glucose concentration too quickly. **We are not looking for perfect control at this time.**
- Ideally the blood glucose concentration should not drop <8 mmol/L over the entire day and should be >10 mmol/L before the next dose of Caninsulin is due. The dog is ready to go home on this dose if the initial response is satisfactory.
- If there is an excessive glucose-lowering response to the insulin, decrease the insulin dose by 10% and continue monitoring.
- The insulin dose at home should remain the same as at discharge for minimum 1 - 3 weeks, or until the owner has established the treatment and feeding routine at home, unless hypoglycaemia is suspected.
- Schedule a revisit for 1 - 3 weeks' time to reassess clinical signs and to perform blood glucose measurements: Refer to **'Monitoring diabetic control'** and **'Insulin dose adjustments'.**

Monitoring diabetic control

Hospitalised pets invariably have different feeding and exercise patterns, and the stress of hospitalisation can interfere with glycaemic control. Uncomplicated diabetics are better stabilised at home where a normal routine can be established.

Home monitoring

Because the primary goal of Caninsulin therapy is to achieve resolution of clinical signs, it is therefore important to regularly monitor signs such as water consumption and bodyweight.

- Owners should keep a record every day of their pet's appetite and general demeanour, particularly noting any lethargy. At least once a week, they should also measure and record 24 hour water consumption.

Urine testing

- Urine dipstick testing can be helpful to detect diabetic instability, for example, ketonuria may warn of impending illness.
- It is a good idea to have owners of a diabetic pet obtain a dipstick reading for glucose and ketones from a random urine sample at least once a week. It is preferable that glucosuria is present at least some of the time, because persistent negative urine glucose measurements may indicate increased risk for hypoglycaemia and neuroglycopenia.
- It is recommended that the insulin dose is decreased in all animals with consistently negative glucosuria for 1 or more weeks[12,14].
- The dose of insulin should never be increased based solely on positive urine glucose results. Urine glucose correlates very poorly with blood glucose and does not determine the degree of glycaemia.
- The clinical history of the patient's general demeanour, appetite, 24 hour water consumption and weekly urine dipstick readings help to assess clinical control. **Accurate interpretation of blood glucose curves is not possible without this information[13,14].**

Monitoring diabetic control

- Encourage owners to keep a home log.
- Monitor appetite and general demeanour daily.
- Monitor 24 hour water consumption and urine dipstick reading at least once a week.
- Never increase the insulin dose based only on positive urine dipstick results.
- **Accurate interpretation of blood glucose measurements is not possible without information from physical examination and clinical history, including the owner's records on the animal's general demeanour, appetite, water consumption, etc.**

Insulin dose adjustments

The insulin dose should only be increased if all of the following conditions are met:

- Some improvement of clinical signs (that is, decreased water intake, decreased urine output, weight gain, decreased polyphagia, and/or increased activity/interaction) was clearly demonstrated with lower insulin doses.
- Some clinical signs of diabetes are still present (for example, polyuria, polydipsia, lethargy, polyphagia).
- There is evidence that blood glucose is often above the renal threshold (for example, based on blood glucose measurements in the clinic or at home, or based on consistently positive urine glucose measurements at home).

Blood glucose curves

A blood glucose curve represents the results of a patient's serial blood glucose concentrations measured at regular intervals throughout the day, starting just before the morning insulin dose. The results are then plotted against time to produce a curve. **Note that sporadic, single blood glucose measurements provide little useful clinical information for monitoring glycaemic control[13]. Many experts on pet diabetes management recommend that no line is drawn to 'join the dots' of a blood glucose curve because the blood glucose concentration does not necessarily travel in a straight line between measurements.**

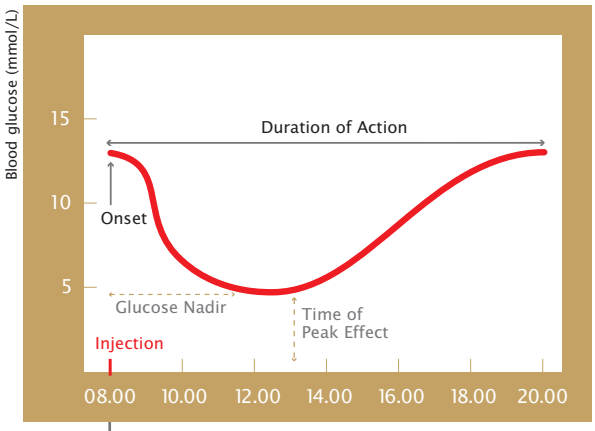
Patient reassessment is recommended every 1 - 3 weeks after initiating therapy until clinical signs have resolved and the dose remains unchanged for 2 consecutive examinations. When evaluating a diabetic patient for dose adjustments, as emphasised previously, it is important to interpret blood glucose curves in conjunction with a physical examination of the patient (including weight), and to review the owner's home log regarding appetite and general demeanour, signs of lethargy, 24 hour water consumption and urine dipstick measurements.

There can be significant day-to-day variability between glucose measurements despite patients receiving the same insulin dose and meal[13]. The reasons for inter-day variability may be attributed to variations in the amount of insulin administered, insulin absorption, availability of insulin in the plasma to the insulin receptors, the level of peripheral insulin sensitivity, variations in food intake, and physical activity. Unfortunately, the main causes of variability are patient-related and cannot be controlled. Because of daily variability, the results of blood glucose measurements should always be interpreted conservatively.

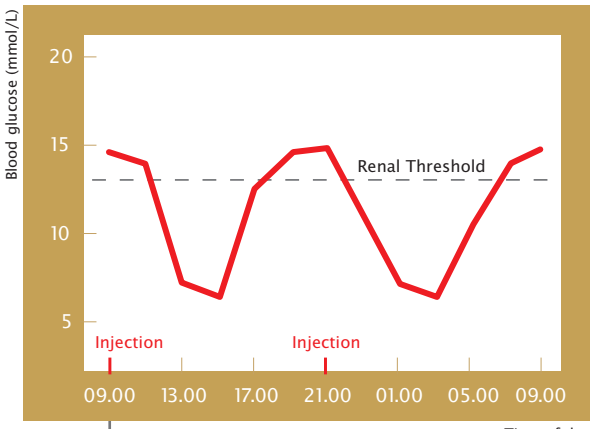
In the clinic setting, cats can potentially experience an acute elevation in blood glucose known as stress hyperglycaemia. If this occurs, it is very difficult for an accurate blood glucose curve to be produced.

Protocol to generate a blood glucose curve

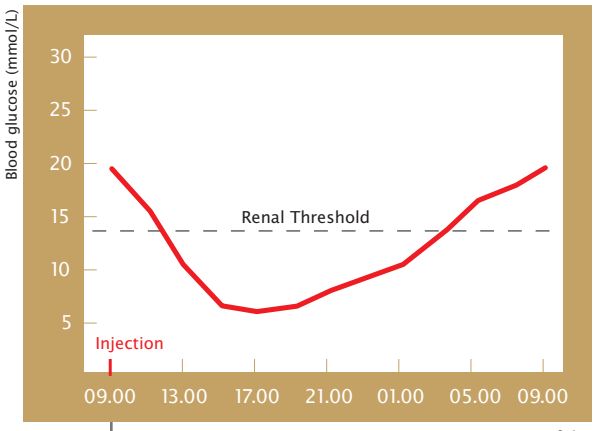
- Obtain a baseline blood glucose measurement.
- Have the owner administer the usual Caninsulin dose and meal. If the owner administers the Caninsulin, it provides a good opportunity to review injection technique and insulin handling. Correct any problems. If the patient will not eat, take the pet to a less stressful environment and return to the clinic before the next blood glucose measurement is due.
- Aim to obtain blood glucose measurements every 1 - 2 hours, ideally until the next insulin injection is due. Minimise stress and follow the normal feeding and exercise routine as closely as possible while the patient is in the clinic.
- Plot the blood glucose curve.



Graph 1: Example of a blood glucose curve in a diabetic dog.



Graph 2. Blood glucose curve in a dog receiving twice-daily administration of Caninsulin.



Graph 3. Blood glucose curve in a dog receiving a once-daily administration of Caninsulin.

Check the following on the plotted graph:

- The baseline blood glucose – resting blood glucose concentration just before insulin administration.
- The nadir – lowest blood glucose concentration obtained.
- The pre-insulin blood glucose – the last measurement just before the next dose of insulin is due to be given.

If evaluation of clinical signs supports good diabetic control and a patient's nadir falls within the range of 5 - 9 mmol/L, and both the baseline and pre-insulin blood glucose values are greater than 10 mmol/L, the patient is likely to have optimal clinical control.

Interpreting blood glucose results

Blood glucose concentration	Recommended action
Nadir <3 mmol/L	Higher dose decreases (50%) may be required for these instances[18]*
Clinical signs of hypoglycaemia	Higher dose decreases (50%) may be required for these instances[18]*
Nadir between 3 - 5 mmol/L	Decrease dose by 10% (dogs) Decrease by 1 IU (cats)[12]
Pre-insulin blood glucose <10 mmol/L (dogs) Pre-insulin blood glucose <15 mmol/L (cats)	Decrease dose by 10% (dogs) Decrease by 1 IU (cats)
Nadir between 5 - 9 mmol/L and Pre-insulin blood glucose for dogs >10 mmol/L Pre-insulin blood glucose for cats >15 mmol/L	No Change
Nadir >9 mmol/L and Pre-insulin blood glucose values >15 mmol/L	If clinical signs present, increase dose by 10% (dogs) Increase by 1 IU (cats)
Return to baseline glucose level too soon indicating duration of insulin action too short	Increase frequency of insulin administration (only for dogs currently on once-daily administration)

* After resolution of the hypoglycaemic event, subsequent adjustment to establish the maintenance dose should be made by increasing or decreasing the daily dose by approx. 10% (depending on the evolution of clinical signs and evolution of serial blood glucose measurements).

- Insulin dose adjustments should be made conservatively. Where indicated, dose increases should be made at 1 - 3 week intervals and at no greater than 10% increases at a time for dogs and 1 unit at a time for cats.
- For cats, ideally no more than 2 units per injection should be administered in the first 3 weeks of treatment.
- The dose of Caninsulin should be rechecked, and adjusted if necessary, every 1 - 3 weeks until clinical signs are resolved and the dose is unchanged on 2 consecutive visits. Then re-evaluate the patient's progress by reviewing the owner's home records at least once a month.
- If water intake is >60 - 70 mL/kg/day for dogs or >30-40 mL/kg/day for cats, or the diabetic patient is lethargic or losing weight, then blood glucose reassessment is indicated, as adjustment of the patient's insulin dose is probably required.
- If persistent negative glucosuria is recorded, it is also prudent to re-evaluate the insulin dose.

When to re-evaluate for insulin dosage adjustments

- Every 1 - 3 weeks during initial treatment period
- Water intake >60 - 70 mL/kg/day for dogs or >30-40 mL/kg/day for cats
- Signs of lethargy
- Weight loss
- Change in appetite
- Persistently negative glucosuria
- Anytime neuroglycopenia is suspected

Signs of good glycaemic control

- Water consumption <60 - 70 mL/kg/day for dogs, or <30-40 mL/kg/day for cats
- Normal appetite
- Stable bodyweight
- Alert and active pet
- No ketonuria

What to feed the diabetic patient

Good glycaemic control is dependent upon a controlled and consistent dietary intake. Day-to-day variations in the timing, amount, and carbohydrate content of food should be minimised in order to maintain consistency and avoid postprandial hyperglycaemia.

Diets should be individually tailored to suit each diabetic patient. Diets should be palatable, nutritionally balanced, provide sufficient calories tailored to individual needs, and provide consistent carbohydrate content. As this is difficult to accomplish with home-prepared meals, commercial pet food is often preferable.

Abnormalities in body condition should be addressed when formulating a diet plan. Thin patients should gain weight and obese patients should lose weight. Weight reduction in obese diabetic patients requires careful reduction of caloric intake after pathological weight loss has been arrested. In general, reduction of intake to 60–70% of caloric requirements for ideal bodyweight will facilitate weight loss.

Another important consideration when formulating a diet plan for a diabetic patient is the presence of concurrent disease, for example renal failure or pancreatitis. These patients will have specific dietary needs depending on the disease and should take precedence when tailoring a diet plan.

For both dogs and cats, clean drinking water should be available at all times. A reduction in excessive water consumption indicates successful management of the diabetes mellitus.

Dogs

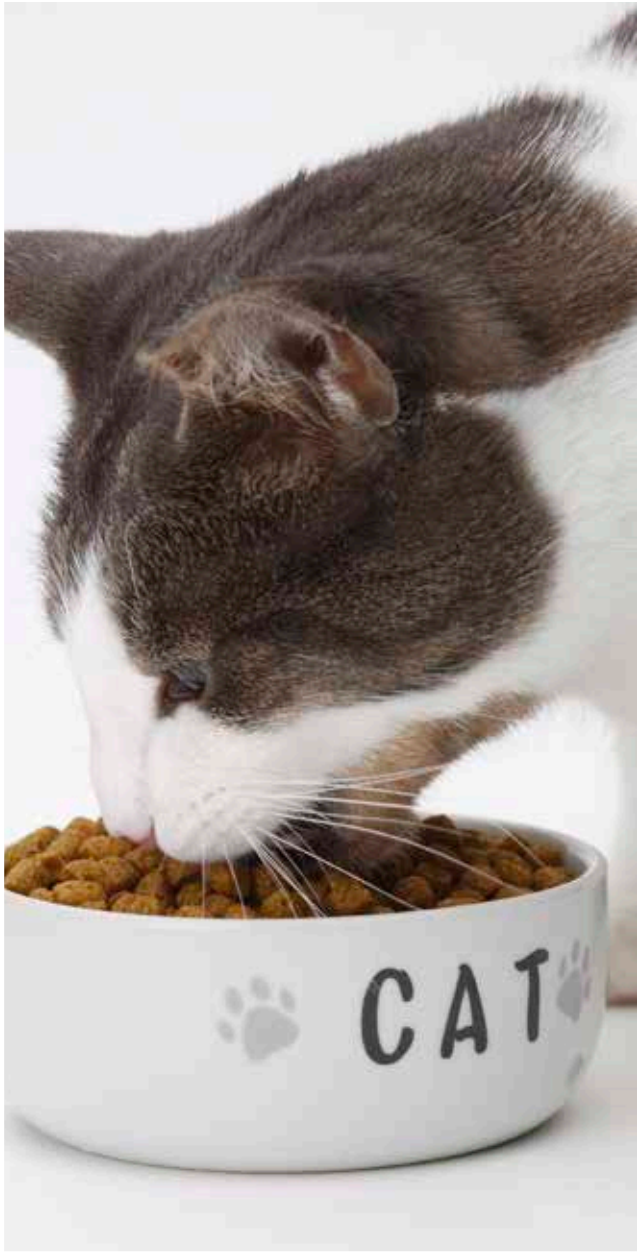
- Dogs are susceptible to postprandial hyperglycaemia and therefore the timing of feeding is important to maintain consistency and good glycaemic control.
- For dogs receiving twice-daily Caninsulin therapy, good glycaemic control can be achieved by feeding two meals a day, half their daily ration with each insulin administration.
- Dogs receiving once-daily Caninsulin therapy can be fed one half of their daily ration just prior to the insulin injection and the remainder approximately 7.5 hours later.

What to feed diabetic dogs:

- Palatable
- Nutritionally complete and balanced
- Provide appropriate quantity of calories
- Consistent carbohydrate content
- Address individual needs (e.g. concurrent disease)
- Consistent amount and type of ingredients, and consistent timing

Cats

- Cats are not susceptible to postprandial hyperglycaemia when fed typical feline diets. Therefore, the timing of eating relative to insulin administration is not as important as it is for dogs. Many cats prefer to graze throughout the day rather than consume their food in one sitting.
- Obesity is a major contributor to the development of diabetes mellitus in cats, and restoration of a normal bodyweight in conjunction with good glycaemic control may allow some diabetic cats to go into remission[12]. A high–protein, low–carbohydrate diet may improve diabetic control and increase the likelihood of remission. Obese cats that tend to devour their food should have their rations divided as described for dogs on twice-daily therapy.
- Cats are often very fussy eaters and usually prefer to eat when they choose. Free access to a measured amount of food is often the best option. Diabetic cats can be managed on their usual diet if need be, but if the cat will accept them, diets low in carbohydrate are usually preferred. In general, most wet cat foods have low dietary carbohydrate content and most dry cat foods have high dietary carbohydrate content. The exceptions are prescription dry foods formulated for diabetic cats.



What to feed diabetic cats

- Palatable
- Provide appropriate quantity of calories
- Nutritionally complete and balanced
- High–protein, low–carbohydrate e.g. wet cat foods or prescription dry foods formulated for diabetic cats
- Address individual needs (e.g. concurrent disease)

Trouble-shooting problem diabetics

The poorly controlled diabetic patient will have clinical signs that are associated with either or both of the following:

- Hyperglycaemia (i.e. polyuria, polydipsia, polyphagia, weight loss) or
- Neuroglycopenia (inappetence, restlessness, negative glucosuria, shivering, disorientation etc.)

Before embarking on an investigation of the cause of the poor diabetic control, owner compliance issues should be reviewed.

A. Owner compliance issues

Examine the patient's home log and obtain a history from the owner to determine whether the clinical signs noted are consistent with either hyperglycaemia or hypoglycaemia.

Check owner compliance with regards to:

- Diet (consistent amount, type of ingredients and timing)
- Exercise (consistent routine)
- Timing of injections (is the insulin being given at the correct time?)

It is also useful to review the way Caninsulin is being stored and handled and to actually watch the product being administered by the owner.

Storage and handling problems

- Check that Caninsulin is being stored correctly (refrigerated, not frozen; no solid particles that will not resuspend with thorough mixing) and is within its expiry date. Once opened, a vial/cartridge should be used within 6 weeks. Check that the owner is correctly resuspending the insulin before administration (shaking the vial thoroughly until a homogenous, uniformly milky suspension is obtained). If there is any doubt regarding the efficacy of the insulin due to poor storage techniques then restart therapy with a new vial/cartridge and evaluate the patient in 2 weeks' time.
- Watch the owner's technique for drawing up and administering the injection.
- Ensure that the correct syringes are being used. Check that the owner has the correct syringe size, and that a new syringe is being used for every injection.
- Check that they draw up the correct volume of insulin into the syringe, expelling the air and then successfully injecting the patient subcutaneously (not intradermally).
- Check that different injection sites are being used for each injection.
- Ensure that the person you are evaluating is the person that normally administers the insulin.
- For administration problems with Caninsulin VetPen refer to the product label. It is especially important to ensure that the VetPen is being primed correctly prior to every injection.

B. Clinical hyperglycaemia

If the patient still has persistent clinical signs associated with hyperglycaemia (polyuria, polydipsia, polyphagia, weight loss) and good owner compliance with treatment has been confirmed, it is appropriate to conduct a full clinical examination and to perform blood glucose measurements.

There are several reasons why diabetic patients may have persistent clinical signs of hyperglycaemia. These include problems with insulin administration and storage (see product leaflet for details), absorption from the site of injection, inadequate or excessive dosing, and poor insulin sensitivity with concurrent disease complications.

Insulin absorption problems

- Delays in absorption from the site of injection will affect the product's efficacy: a clue to this may be the nadir appearing later in the patient's blood glucose measurements. Check for thickening and fibrosis at the usual injection sites. Correct any dehydration with fluid therapy and change injection sites if there is evidence of fibrosis.

Inadequate insulin dose

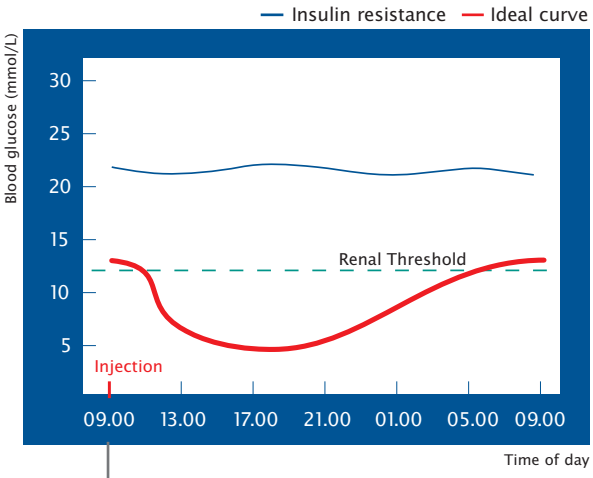
- Insufficient insulin dose will result in the patient's blood glucose concentrations remaining above the renal threshold for most of the day and persistent clinical signs. See Graph 4.

In cases of hyperglycaemia due to inadequate insulin dose refer to the section **'Insulin dose adjustments'.**

Insulin resistance

In both dogs and cats insulin resistance should be suspected when:

- There is failure to control the clinical signs of diabetes despite a dose of greater than 1.5 IU/kg bodyweight every 12 hours[12,15].



Graph 4: Example of inadequate insulin dose, with normal response for comparison

Insulin resistance due to excessive insulin dose

Excessive insulin dosing can induce chronic hyperglycaemia through poorly understood mechanisms. One explanation is that high insulin dosing induces hypoglycaemia, which stimulates an excessive and prolonged counter-regulatory hyperglycaemic response (Somogyi effect). As the blood glucose falls below the normal range, diabetogenic hormones are released. The blood glucose rises, often dramatically, because there is not enough endogenous insulin to blunt the diabetogenic response. The inciting hypoglycaemic episode is not readily detected by standard blood glucose monitoring and might occur overnight. The hyperglycaemia appears to persist for several days and can be compounded by repeated overdosing.

Affected patients are hyperglycaemic most of the time and show persistence of clinical signs. These cases are often perceived incorrectly as a failure to respond to insulin and consequently the insulin dose is increased. The possibility of insulin-induced hyperglycaemia should be considered whenever there is failure to improve with increases of the insulin dose.

The key to diagnosing Somogyi in diabetic dogs and cats is documenting improvement of diabetic control when the insulin dose is decreased. Substantial improvement can often be achieved with small adjustments of the insulin dose; often with a decrease of just <10% for dogs and 1 IU for cats. The improvement can be immediate or may be gradual over 1 - 2 weeks. In contrast, dogs and cats with poor diabetic control due to an inadequate insulin dose will typically become much more polydipsic and polyuric within 12 hours of such a trial decrease of their insulin dose. This immediate worsening of clinical signs will confirm that Somogyi was not the reason for poor diabetic control in those cases, and the previous insulin dose can be promptly resumed and the investigation for another cause continued.

Close attention to the animal's clinical signs may allow a clinical suspicion that Somogyi is occurring. There is typically a history of good diabetic control for a variable period, which might be very brief or may not have been noted in the patient's records if the owners did not contact their veterinarian when their pet was 'going well'. It is important to check if the insulin dose was the same or lower than the current dose during that period. Deterioration of diabetic control often

Typical concurrent problems causing insulin antagonism

- Obesity
- Recurrent infections (cystitis, pyoderma, periodontitis, prostatitis)
- Neoplasia
- Organ disease (renal failure, chronic pancreatitis)
- Hyperthyroidism/hypothyroidism
- Acromegaly (hypersomatotropism)
- Dioestrus or pregnancy

begins with intermittent polydipsia, especially overnight, which sometimes follows a 3-day cycle. The owners might also report unusual behaviours, pacing/restlessness, yowling, vomiting, urinating, etc., especially in the early hours of the morning. In some cases, hypoglycaemia may have been recorded or suspected, and then disregarded as an error.

If the early signs are missed, animals experiencing recurrent Somogyi will present as having 'brittle' diabetic control or insulin resistance. **The possibility of insulin overdose causing recurrent Somogyi should be considered for all diabetic dogs and cats presenting with insulin resistance.** These patients show clinical signs of poor diabetic control such as polydipsia and polyuria. They may present with very unpredictable blood glucose results that vary anywhere from 1.5 - 35 mmol/L despite consistent insulin dosing. Key factors include failure to improve with increases of the insulin dose, and sometimes weight gain despite otherwise suboptimal diabetic control.

Patients with blood glucose measurements that have a rapid drop of blood glucose over a short period of time, followed by a rapid rise, may also be experiencing an excessive insulin dose. First check that you are not overdosing by decreasing the dose and evaluating the patient again in 2 - 4 weeks' time, to see if there is a longer duration of action and an improvement in clinical signs such as a reduction in water consumption.

Insulin resistance due to medication

Concurrent administration of medications such as corticosteroids and progestagens (e.g. megestrol acetate) will interfere with insulin action.

Insulin resistance due to concurrent disease

Most diabetic patients are middle-aged to geriatric; consequently many suffer from concurrent diseases that may interfere and cause insulin resistance (see table on opposite page). If concurrent disease is suspected then further investigation for possible causes is warranted.

C. Neuroglycopenia

Neuroglycopenia (clinical hypoglycaemia) may occur at any stage, especially when there is good diabetic control. Owners are less likely to contact their veterinarian during periods when their pet is 'going well' and might relax their home monitoring routine, thus increasing the chances that early signs might be missed. Clinical signs range from hunger initially, then inappetence, restlessness, weakness and shivering, to disorientation and collapse, seizures and coma. Trembling also occurs in dogs and yowling in cats. Some animals will vomit. This condition may be due to insulin overdose, but may also be triggered by such events as loss of appetite, vomiting, excessive exercise or administration of insulin at irregular intervals.

Correct any owner compliance issues then thoroughly investigate the following other potential causes of hypoglycaemia.

Insulin overdose

- Relative insulin overdose causes hypoglycaemia. Resolution of these signs following a meal or glucose administration supports a tentative suspicion for hypoglycaemia, although a blood glucose measurement at the time is required for confirmation.

Hypoglycaemic patients generally require a reduction in the dose of insulin; refer to the table on Page 15 for recommended dose adjustments.

Concurrent disease

- Concurrent disease that increases the risk of hypoglycaemia includes exocrine pancreatic insufficiency (EPI), hepatic insufficiency, and any disease that may cause inappetence. If disease is suspected then further investigation for possible causes is warranted.

Remission

In diabetic cats, hypoglycaemia may herald diabetic remission.

Inappetence in a diabetic patient usually means that concurrent disease is present, and the dog or cat should be examined by a veterinarian as soon as possible.

If the diabetic patient is to be fasted, for example prior to elective anaesthesia, it is recommended that a lower dose of insulin (approximately 50% of the normal dose) is administered at the usual injection time.

Management of hypoglycaemia

At home	In the clinic
▪ Feed a meal. Note that meal feeding will only work for dogs. Cats do not have reliable postprandial hyperglycaemia when fed cat foods. However, they cannot taste sweet foods, so glucose syrup or honey can be mixed with cat food to treat hypoglycaemia. ▪ Administer glucose syrup or solution into the side of the mouth. ▪ If the animal is seizuring, glucose syrup can be administered per rectum.	▪ Administer glucose syrup or solution into the side of the mouth. ▪ 1 mL/kg 50% dextrose diluted in an equal volume of saline, given intravenously. ▪ If the animal is seizuring, glucose syrup can be administered per rectum.

Summary protocol

Initial stabilisation

- Ensure you have an accurate diagnosis.
- Measure blood glucose over the first day to ensure no hypoglycaemia.
- Decrease the insulin dose if nadir <5 mmol/L, or pre-insulin blood glucose for dogs <10 mmol/L or <15 mmol/L for cats.
- Ensure client is fully informed and happy with injection technique/VetPen use and feeding regimen.
- Discuss with the owner that it may take several months to achieve very good diabetic control.

Dogs

– 0.25 - 0.5 IU/kg Caninsulin every 12 hours or

– 0.5 IU/kg Caninsulin once-daily

Cats

– 0.25 - 0.5 IU/kg Caninsulin every 12 hours (ideally no more than 2 IU per injection in the first 3 weeks of treatment)

Assessing diabetic management

- Re-evaluate the patient every 1 - 3 weeks.
- Review the owner's log (appetite, demeanour, water consumption, urine dipstick) and question the owner regarding improvements - resolution of clinical signs suggests successful management.
- Perform a though clinical examination and weigh the patient.
- If indicated, perform a serial blood glucose curve. Accurate interpretation of blood glucose measurements is not possible without information from a physical examination and clinical history, including the owner's records on the animal's general demeanour, appetite, water consumption, etc.
- The insulin dose should only be increased by approx. 10% if all of the following conditions are met:
  - some improvement of clinical signs (that is, decreased water intake, decreased urine output, weight gain, decreased polyphagia, and/or increased activity/interaction) was clearly demonstrated with lower insulin doses
  - some clinical signs of diabetes are still present (for example, polyuria, polydipsia, lethargy, polyphagia)
  - there is evidence that blood glucose is often above the renal threshold (for example, based on blood glucose measurements in the clinic or at home, or based on consistently positive urine glucose measurements at home)
- Do not alter the dose more frequently than every 1 - 3 weeks unless hypoglycaemia is suspected.
- When evaluating a patient for poor response to insulin treatment, always check for administration and storage problems first, then for possible insulin resistance due to excessive dosage - if in doubt decrease the dose by 10% for routine cases.

Addressing client difficulties with injections

The **Caninsulin VetPen** offers an innovative, user-friendly means to help pet owners administer Caninsulin to their pet.

Simplifies client counselling

Sleek pen design is less threatening and may ease client anxiety or resistance to starting treatment of their diabetic pet:

- Less impact on clients' lifestyle.
- Easier for clients when out and about.
- Insulin delivery can be explained easily.
- Less preparation before administration.
- Reduces opportunity for dosing errors.

Improves dosing accuracy

- Dose selector dial allows accurate dosing every time.
- Dosing accuracy is less reliant on clients' vision or dexterity.
- Reusable insulin cartridge provides multiple doses with minimal preparation.
- Reduces chance of contamination after first use.

Enhances administration safety

- Double needle caps and needle remover lower the risk of accidental needle-stick injury.
- Sturdy, cartridge-within-holder design reduces likelihood of breakage.

Ergonomic design

- Easier for users to handle.
- Accessories such as the Dose Selector Adaptor and Release Button Extension enhance user control.

Precision instrumentation

- Facilitates insulin dose measurement.
- Improves dosing accuracy and precision.
- Reduces the chance of air bubbles that may lead to inaccurate dosing.

The VetPen is available in two sizes:

- 0.5 - 8.0 IU with 0.5 IU incremental adjustments
- 1.0 - 16.0 IU with 1.0 IU incremental adjustments

Caninsulin for use in the VetPen is presented as a 2.7 mL cartridge.

Caninsulin VetPen starter kit includes:

Quick Pen Components Guide

- Simple, illustrated diagram that shows Caninsulin VetPen components and accessories.

Client Instruction Booklet

- Easy-to-follow, step-by-step instructions with photos that show clients how to load, use, and store the pen.

Needle Remover

- Device that allows for safe removal of needles from the pen.

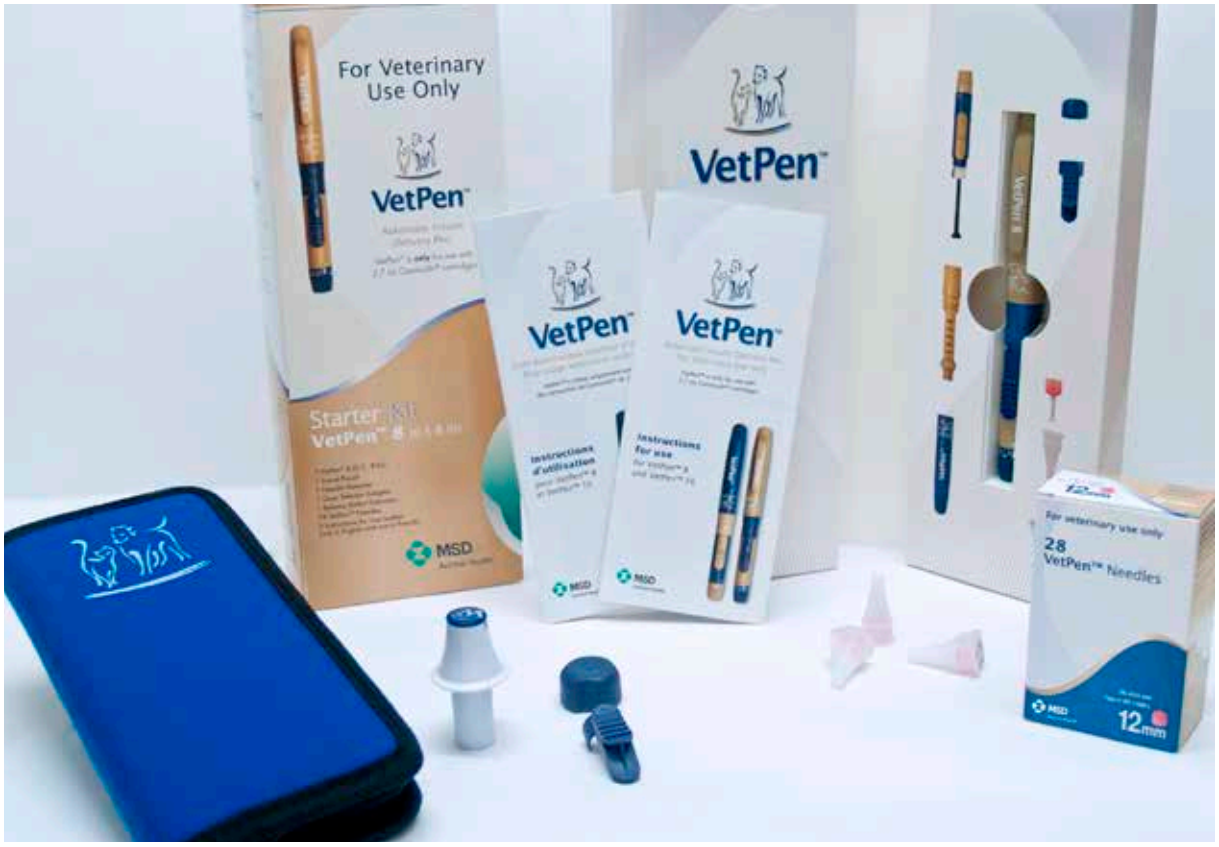
28 Needles

- A generous supply of VetPen needles to get clients started. These ultra-thin pen needles feature a silicone coating to minimise discomfort at injection.

Travel Pouch

- Flexible pouch holds pen, needle, needle remover and insulin.

NOTE: Caninsulin cartridges are sold separately.



Frequently asked questions about Caninsulin and Caninsulin VetPen

VetPen

With the development of VetPen, MSD Animal Health is proud to bring the advances of human diabetes management to veterinary practice.

What makes VetPen unique?

- More convenient to use than insulin vials and syringes.
- Easier to precisely deliver an accurate dose consistently over time, with less chance of error. Accurate doses of insulin can be selected down to 0.5 IU.
- Provides a better fit to clients' lifestyles - it takes fewer steps to prepare doses once primed (air removed from cartridge) and can be used discreetly anywhere.

Is VetPen difficult to use?

VetPen features a user-friendly design for easy handling, preparation, and injection. In a 3-week study, close to 97% of pet owners reported that VetPen is easy to use overall[16]. Additional adaptors are provided to further assist users with visual or manual dexterity issues.

Is VetPen more accurate than using an insulin syringe?

Yes. In a laboratory study, VetPen was found to have a higher dosage accuracy, particularly for animals on low insulin doses[17]. Unlike syringes, VetPen provides an accurate dose every time, without relying on the user's ability to draw up a dose accurately[17].

Can the dose selector be turned in both directions?

No. The dose selector is designed to move from low to high numbers, but cannot be moved from high back to low numbers. If too high a dose has been selected, it is very important not to try to turn the dose selector back to a lower dose. This can damage or break the VetPen. If too high a dose has been selected, release the insulin through the needle into a tissue or swab by pressing the release button. Then select the correct dose - be sure to turn the dose selector carefully to ensure accurate dose selection.

Can VetPen be used with other insulin products?

No. VetPen must be used with specially designed 3 mL cartridges which contain 2.7 mL of Caninsulin, a 40 IU/mL insulin. To avoid damaging VetPen and dosing errors, cartridges containing other insulin should not be used with VetPen.

Do I need to keep VetPen refrigerated when it contains an insulin cartridge?

Store unopened Caninsulin VetPen cartridges in an upright position in the refrigerator. After first opening, Caninsulin VetPen cartridges may be refrigerated for up to 6 weeks; in-use cartridges do not need to be stored upright. At all times cartridges should be protected from light.

Is VetPen reusable?

Yes. VetPen contains an insulin cartridge that allows multiple doses to be provided with minimal preparation time. When all the insulin has been used, simply remove the empty cartridge and insert a new one. Please note that sterile needles are designed for single use only and should not be reused.

What types of needles are used with VetPen?

VetPen uses specific 29G/12 mm needles, which are small, thin, triple-sharpened, and specially lubricated to lower penetration force and minimise pet discomfort. These are the only needles that should be used with VetPen. Always use a new, sharp, sterile needle for each injection. A blunt, used or bent needle may cause discomfort and possible infection for the pet. Dispose of used needles in a suitable sharps/biohazard container.

Caninsulin

Can I dilute Caninsulin?

No. The product should not be diluted as it will change the relative amounts of the amorphous and crystalline fractions. The pharmacodynamics and pharmacokinetics of the product will be altered if these fractions are changed in any way.

Can pet owners reuse insulin syringes?

This is not recommended as Caninsulin does not contain any preservatives, therefore if an owner contaminates the bottle by reusing a syringe, this will potentially reduce the product's efficacy.

Can I use Caninsulin for the initial treatment of patients with diabetic ketoacidosis (DKA)?

Caninsulin is not recommended for the treatment of diabetic ketoacidosis.

For how long can an owner use a broached vial of Caninsulin or VetPen cartridges?

Any unused portion of the vial/cartridge should be discarded after 6 weeks.

General

What presentations are Caninsulin and VetPen available in?

Caninsulin vials are available in two sizes (2.5 mL and 10 mL).

For administration, 0.5 mL and 1 mL 40 IU/mL (U-40) syringes are available.

Caninsulin VetPen cartridges contain 2.7mL of Caninsulin and are available in packs of 10.

VetPen Starter Kits are available in 0.5 - 8.0 IU (VetPen 8 Starter Kit) and 1.0 - 16.0 IU (VetPen 16 Starter Kit); VetPen needles are available in packs of 100.

What support tools does MSD Animal Health offer veterinarians and pet owners?

- Product leaflet that is provided inside the outer carton.
- Owner's manual providing helpful advice for owners of diabetic pets and an example of a data sheet for patient home monitoring.
- Information on diabetes, Caninsulin and VetPen training videos available at: www.caninsulin.com
- A team of Technical Services Veterinarians to provide advice on the management of diabetic cases - phone 1800 033 461.
- Caninsulin VetPen training app available for iPad - just search 'VetPen' in the App Store on your iPad.
- Additional VetPen support materials also available at: http://www.caninsulin.com/vetpen/about-vetpen.asp

Notes

Notes

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For more information go to
www.caninsulin.com

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