

## WHAT INSULIN ARE WE USING IN DOGS THIS WEEK?

*Patty A. Lathan, VMD, MS, DACVIM*

*Louisiana State University, Baton Rouge, MS, USA*

The goals of treating diabetes include improvement of the patient's (and owner's) quality of life, control of clinical signs, and avoidance of complications from diabetes (such as diabetic ketoacidosis) and from over-treatment with insulin (hypoglycemia). Proper treatment includes identifying and treating or eliminating any cause of insulin resistance (infection, obesity, etc.), dietary management, and insulin therapy.

### Diet

Although high fiber diets have been recommended in dogs, they are not ideal for all diabetics. High fiber diets tend to cause weight loss, which is undesirable in dogs that are underweight or at an ideal body weight. In these dogs, a high quality maintenance dog food with a moderate fiber content is preferred. Canned diets and other diets lower in carbohydrate content may help with post-prandial hyperglycemia.

### Insulin Therapy

Historically, dogs have been treated with twice-daily insulin injections using intermediate-acting insulins. Lente (Vetsulin®) and NPH (Neutral protamine Hagedorn, either Humulin N® or Novolin N®) have most frequently used for first-line therapy (0.25 – 0.5U/kg BID). Glargine and detemir have also been evaluated for use in dogs, and detemir is useful when the duration of lente or NPH is too short. Remember that detemir is more potent in dogs than in people, so a starting dose of 0.1 U/kg BID is recommended. Unfortunately, detemir is no longer available.

Once daily PZI (ProZinc®) at a starting dose of 0.5 U/kg has also been approved by the FDA for use in dogs; anecdotal evidence suggests that a starting dose of 0.7 U/kg SID may result in faster diabetic control.

### Advancements in Basal Insulins

Basal insulins are increasingly utilized because they offer lower day-to-day glycemic variability compared to porcine lente insulin when administered twice daily, and they are less likely to result in clinical hypoglycemia, particularly in inconsistent eaters.

- **Insulin Degludec (U-100 or U-200):** This insulin forms multi-hexamers in the subcutaneous tissue, allowing for a very slow release of monomers. A study indicated that up to 85% of dogs might be controlled on an SID basis, though clinical experience suggests a success rate closer to 50–60%. For insulin-naïve diabetics, the recommended starting dose is 0.5 U/kg q24h.
- **Glargine U-300:** This is a highly concentrated form of glargine. Because its microprecipitates have less surface area, it results in smoother, slower absorption and a longer duration of action than the U-100 formulation. It must be administered via an insulin pen. Research shows that

roughly 59% of dogs can be maintained on SID dosing, while 41% may still require BID administration for optimal control.

### **Monitoring and Clinical Success**

**Clinical signs are the most important part of monitoring diabetics.** A daily log of water intake, urination frequency, appetite, and body weight provides more insight into the patient's true status than a single blood glucose curve.

Glycemic monitoring is recommended to allow insulin dose increases while avoiding hypoglycemia. Continuous glycemic monitoring using the **FreeStyle Libre (FSL)** is recommended in general, but is almost required when starting a dog on a basal insulin. The FSL identifies trends and hypoglycemic events that traditional curves might miss due to significant day-to-day variation. However, the FSL is not always accurate, especially in the lower ranges, so confirming low values with a glucometer is recommended.

## **SGLT2-inhibitors for the Treatment of Feline Diabetes Mellitus**

Patty Lathan, VMD, MS, DACVIM  
Louisiana State University

Diabetes mellitus (DM) is one of the most common endocrinopathies in cats. Dietary management and twice-daily insulin have been the mainstay of therapy for decades. Unfortunately, up to 30% of feline diabetics are euthanized at or within one year of diagnosis. While many cats experience a good quality of life with insulin therapy, disruption of the owners' schedules, needle phobia, and concern over potential hypoglycemia can decrease overall owner satisfaction.

Sodium glucose co-transporter-2 (SGLT-2) inhibitors such as empagliflozin and dapagliflozin have been used to treat type 2 diabetes mellitus (T2DM) in humans for over ten years. They work by decreasing renal re-absorption of glucose, resulting in glucose loss through the urine and subsequent reduced blood glucose concentration (BG). This normalizing blood glucose concentration (BG) allows some remaining pancreatic beta cells to recover from glucose toxicity. These beta cells may then secrete insulin, resulting in less renal filtration and, subsequently, loss of glucose through the kidneys. SGLT-2 inhibitors also have cardio- and reno-protective effects in people.

Within the past few years, two oral SGLT-2 inhibitors (SGLT2i) have been FDA-approved for use in newly diagnosed diabetic cats—velagliflozin and bexagliflozin. Whereas bexagliflozin (Bexacat®) is available in tablet form, velagliflozin (Senvelgo® oral solution) is available as a liquid. Bexagliflozin is dosed as one tablet per cat per day for cats weighing 3kg or more. Velagliflozin is dosed at 1 mg/kg once daily.

Bexagliflozin (bexa) and velagliflozin (vela) have been evaluated in clinical trials, with clinical efficacy in >80% of cats. Whereas only cats that had not been previously treated with insulin were included in the bexagliflozin study (84 cats total), the velagliflozin study (252 cats total) also included some cats that had been treated with insulin previously (38 cats). However, neither medication is FDA-approved for use in cats previously treated with insulin.

Clinical hypoglycemia was not identified in any of the cats in the velagliflozin or bexagliflozin studies, although biochemical hypoglycemia occurred occasionally. The most common side effect in both trials was diarrhea. In most cases, diarrhea was mild and self-limiting. Only two cats were removed from the velagliflozin study (2/252) because of diarrhea, and none from the bexagliflozin study (0/84).

The most severe side effect in both studies was diabetic ketoacidosis (DKA), which occurred in approximately 5% of cats. The majority of the cases in both studies occurred during the first ten days, suggesting the need for close monitoring during this period. In the velagliflozin study, a significantly higher percentage of previously insulin-treated cats (7/38—18%) developed DKA than cats that had not received insulin previously (11/214—5%). In a 2015 study, 6% of cats

receiving insulin developed DKA, also more frequently during the first two weeks of therapy. Thus, DKA occurrence rates are similar between cats receiving insulin and SGLT2i.

The ideal patient for SGLT2i therapy (bexagliflozin and velagliflozin) is an otherwise healthy, uncomplicated diabetic cat that is eating and drinking, hydrated, and has no evidence of decreased appetite, vomiting, or diarrhea. Before treatment with an SGLT2i, a minimum database including complete blood count, serum biochemistry, tT4, urinalysis, fructosamine, and assessment of ketones (blood, plasma, or urine) is indicated for baseline evaluation and to rule out concurrent disease and ketosis.

The primary goals of treating diabetic cats are to control clinical signs, improve quality of life, and avoid complications (including DKA, hypoglycemia, and diabetic neuropathy). Thus, monitoring SGLT2i therapy is aimed at assessing physical exam (PE) and clinical signs, as well as evaluating parameters associated with glucose control and DKA. Owners' active participation is crucial, as decreased appetite, lethargy, and vomiting can be early indicators of ketosis and DKA. Cats should also be monitored for signs of hypoglycemia, including lethargy and neurologic signs; however, no clinical hypoglycemia was reported in the trials.

The first recheck should be performed 2-3 days into SGLT2i therapy. Rechecks on days 2-3, 7, and 14 are primarily used to help identify cats that are developing DKA. PE parameters suggestive of developing DKA include dehydration and weight loss. Ketone measurement is ideally performed using a handheld ketone meter that measures beta-hydroxybutyrate (BHB), the most prevalent ketone in acidotic patients. However, ketones can also be measured using urine dipsticks. In addition to urine, plasma obtained from a centrifuged capillary tube can be placed on the square for ketone measurement on urine dipsticks.

Most cats will have improvement in clinical signs, glucose, and fructosamine within 30 days. If no improvement is seen at 30 days, or ketosis occurs/increases (>trace urine dipstick or >2.4 mmol/L on a handheld meter), SGLT2i should be discontinued, and the cat should be started on insulin therapy.

If a cat develops diarrhea while receiving an SGLT2-i, adding fiber to the diet or changing to a higher fiber diet is a prudent first step. Halving the dose of vela may also decrease diarrhea, and this dose is effective in many cats. I do not have experience decreasing the dose in cats receiving bexa.

Cats that develop DKA while receiving SGLT2-inhibitors usually develop euglycemic DKA (eDKA). eDKA is defined as DKA with a BG <250 mg/dL (sometimes <100 mg/dL) in cats. Consistent clinical signs, in addition to ketosis (on a urine dipstick or BHB on a ketone meter) and acidosis (pH <7.3 on a blood gas), are diagnostic of DKA. Treatment of eDKA is similar to treatment of hyperglycemic DKA. A significant difference is that dextrose is added to fluids initially, and dextrose concentrations >5% in the fluids may be needed. Implementing dextrose and insulin supplementation soon after diagnosis of eDKA is essential for a positive outcome.

These medications should work without changing the diet, and the effect of changing cats receiving SGLT2-i to a lower carbohydrate diet is unknown. If diet change is desired, I recommend waiting until after the first two weeks of receiving the SGLT2-i, as the side effects of the medication are most likely to occur during that time.

Data on remission rates in cats receiving SGLT2-i is lacking. However, the author has seen remission occur in a cat on velagliflozin, and heard of several others on bexa and vela. Remember that the medications work by inducing glucosuria, so assessing glucosuria will not help in determining whether a cat is in remission. The only way to tell will be to discontinue the medication and assess clinical signs and BG over the following week. Even if a cat goes into remission while on an SGLT2-i, there is no evidence that they will become hypoglycemic if they continue receiving the medication. Additionally, continuing the medication may help prevent further progression of pancreatic pathology.

SGLT2 inhibitors have not been approved for use in cats with significant comorbidities. However, one publication reports their successful use in cats with hypersomatotropism. Additionally, I have used these medications successfully in several cases receiving glucocorticoid therapy. In both situations, client education and close monitoring are crucial.

In summary, SGLT2 inhibitors are a promising new once-daily oral treatment option for feline DM. Most cats experience improvement in clinical signs and glycemic parameters within 30 days. Diarrhea is common but usually mild and self-limiting. eDKA is the most severe side effect; although uncommon (5% of ND), proactive monitoring by the owner and veterinary team is crucial for prevention and early detection.