PRACTICAL PHARMACOLOGY

The Role of Sodium–Glucose Cotransporter 2 Inhibitors in Feline Diabetes Mellitus Management

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Until recently, management of feline diabetes mellitus has relied primarily on treatment with insulin, treatment of concurrent illness, and dietary manipulation.[1] A new class of drugs known as sodium–glucose cotransporter (SGLT) 2 inhibitors has become available for treatment of diabetes mellitus in cats.

SGLT2 INHIBITORS

SGLT proteins are a family of membrane proteins, primarily expressed in the proximal tubule of the kidney, that are important mediators of epithelial glucose transport.[2] The SGLT1 protein mediates glucose absorption in the gastrointestinal tract, while the SGLT2 protein is responsible for resorption of the majority of glucose from the glomerular filtrate of healthy animals. The SGLT2 protein in the S1 and S2 segments of the proximal tubule absorbs approximately 90% of the glucose from the glomerular filtrate, while the SGLT1 protein in the S3 segment of the proximal tubule resorbs the remainder of the filtered glucose.[2] Inhibitors of the SGLT2 protein increase urinary glucose excretion by inhibiting glucose uptake in the proximal renal tubule, thereby lowering the blood glucose concentration (**FIGURE 1**). SGLT2 inhibitors improve glycemic control in humans with type 2 diabetes mellitus, without the risk of hypoglycemia. Additional benefits of treatment with SGLT2 inhibitors

Abstract

A new class of drugs known as sodium–glucose cotransporter (SGLT) 2 inhibitors has become available for treatment of diabetes mellitus in cats. These drugs inhibit glucose resorption from the proximal tubule of the kidney, and 2 are now approved by the U.S. Food and Drug Administration for treatment of newly diagnosed feline diabetes mellitus. Bexagliflozin and velagliflozin both decrease blood glucose, decrease fructosamine, and improve clinical signs of diabetes in the majority of newly diagnosed diabetic cats. The most common side effect of treatment with SGLT2 inhibitors is gastrointestinal upset. Diarrhea is the most common gastrointestinal manifestation but is typically mild and self-limiting and responds to symptomatic treatment. The most serious side effect of treatment with SGLT2 inhibitors is diabetic ketoacidosis. This typically occurs within the first 14 days of treatment, and affected cats may be euglycemic rather than hyperglycemic. If diabetic ketoacidosis occurs, treatment with an SGLT2 inhibitor should be discontinued and insulin initiated.

Take-Home Points

- The sodium–glucose cotransporter (SGLT) 2 inhibitors are an exciting new class of drugs in veterinary medicine approved for the treatment of newly diagnosed feline diabetes mellitus.
- Studies suggest that both bexagliflozin and velagliflozin are effective for management of newly diagnosed diabetes mellitus in cats.
- Previously insulin-treated cats are more likely to develop diabetic ketoacidosis when treated with SGLT2 inhibitors.
- Areas that need further study include the role of diet in cats treated with SGLT2 inhibitors and how many cats go into diabetic remission when treated with SGLT2 inhibitors.
- Development of an accurate test to determine the endogenous secretory capacity of the feline pancreas will be important to better predict a positive response of diabetic cats to treatment with SGLT2 inhibitors.

in humans include improvement in insulin resistance, weight loss, a reduction in systolic blood pressure, decreased susceptibility to major adverse cardiovascular events, and a reduction in the rate of progression of chronic kidney disease. Inhibition of the SGLT2 protein does not usually cause hypoglycemia because the SGLT1 protein also absorbs some glucose from the proximal tubule; however, hypoglycemia may occur in the context of coadministration with other antidiabetic agents, such as insulin and sulfonylureas.

SGLT2 INHIBITORS IN CATS

There are 2 SGLT2 inhibitors approved by the U.S. Food and Drug Administration now available for treatment of diabetes mellitus in cats:

- Bexagliflozin (Bexacat; elanco, elanco.com) is a 15-mg flavored oral tablet administered at a dose of 15 mg/cat once a day.[3,4]
- Velagliflozin (Senvelgo; Boehringer Ingelheim, bi-animalhealth.com) is an oral solution also administered once a day at a dose of 1 mg/kg.[5,6]

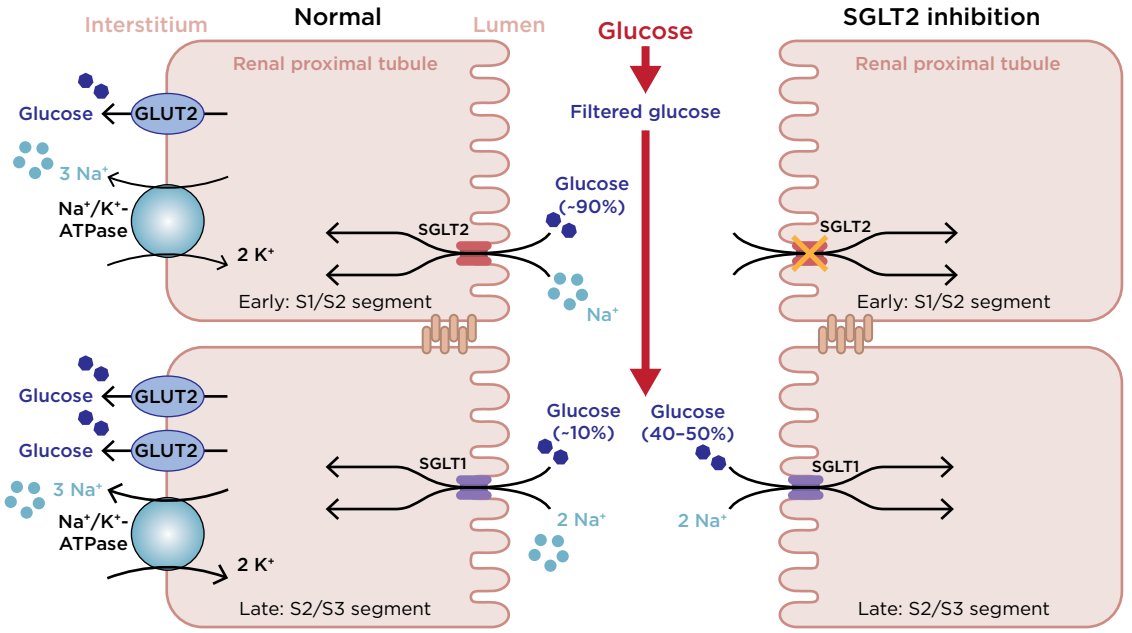

FIGURE 1. Role of renal SGLT2 and SGLT1 in glucose reabsorption in presence and absence of SGLT2 inhibition. The SGLT2 and SGLT1 proteins are expressed in the luminal membrane of the early (S1 and S2 segment) and late (S3 segment) proximal tubule. These proteins reabsorb ~90% (SGLT2) and ~10% (SGLT1) of the filtered glucose load during euglycemia. The capacity of the SGLT1 to reabsorb glucose is upregulated in the presence of SGLT2 inhibition and during hyperglycemia (~40–50% reabsorption).
ATPase = adenosine triphosphatase; GLUT = glucose transporter; SGLT = sodium–glucose cotransporter

Both SGLT2 inhibitors have been shown to cause a rapid decrease in the blood glucose; decrease the fructosamine concentration; and improve clinical signs of diabetes such as polyuria, polydipsia, polyphagia, and weight loss in diabetic cats. It is believed that the rapid and sustained decrease in blood glucose caused by SGLT2 inhibitors resolves glucose toxicity and allows the β cells of the pancreas to increase secretion of some endogenous insulin, which prevents development of diabetic ketoacidosis (DKA). Despite the fact that this drug class induces glycosuria, causing an osmotic diuresis, polyuria and polydipsia improve in the majority of treated diabetic cats.

BEXAGLIFLOZIN FIELD STUDY

In an open-label, historically controlled field study of 84 cats with newly diagnosed diabetes mellitus treated with bexagliflozin, 84% of the 81 evaluable cats were classified as a success based on improvement in glycemic control (mean blood glucose <250 mg/dL on a blood glucose curve or fructosamine <358 µmol/L) *and* improvement in 1 clinical parameter of diabetes mellitus (polyuria, polydipsia, polyphagia, weight loss) on day 56.[4] Polyuria improved in 75% of cats, polydipsia improved in 81% of cats, and polyphagia improved in 63% of the 75 cats that completed the 56-day efficacy study. The most common adverse effects were vomiting, diarrhea, and anorexia, and the most serious adverse effect was DKA, which was reported in 5% of cats.

VELAGLIFLOZIN FIELD STUDY

In an open-label, baseline-controlled field study of 252 newly diagnosed and insulin-treated diabetic cats treated with velagliflozin, blood glucose and fructosamine decreased and clinical signs improved in the majority of cats. Of the 158 cats that completed the 180-day study, glucose and fructosamine were within the reference range at day 180 in >80% of cats; polyuria improved in 90% of cats, polydipsia improved in 88% of cats, and polyphagia improved in 75% of cats.[6] The most common adverse effects were diarrhea and vomiting, and the most serious adverse effect was DKA, which occurred in 5% of naive diabetic cats and 18% of cats previously treated with insulin.

PATIENT SELECTION FOR SGLT2 INHIBITOR TREATMENT

SGLT2 inhibitors are only effective for treatment of diabetic cats with enough endocrine pancreatic function to secrete some endogenous insulin (non–insulin-dependent diabetes mellitus), as insulin is required for glucose uptake into cells and prevention of DKA. Unfortunately, there are currently no reliable tests to distinguish insulin-dependent from non–insulin-dependent diabetes in cats. Because 80% of newly diagnosed diabetic cats are non–insulin dependent and have the capacity to secrete some endogenous insulin, newly diagnosed diabetic cats are the most likely to respond well to treatment with SGLT2 inhibitors.

BOX 1 Criteria for Case Selection

- Newly diagnosed diabetic cat
- No evidence of concurrent illness
- No active pancreatitis
- No urine ketones
- Serum β-hydroxybutyrate <25 mg/dL (2.4 mmol/L)
- No severe renal disease (International Renal Interest Society stage 3 or higher)
- No hepatic disease (i.e., increased liver enzymes, increased bilirubin)

SGLT2 inhibitors are recommended for treatment of cats with newly diagnosed diabetes mellitus that are otherwise healthy and clinically well (**BOX 1**). Cats that have been previously treated with insulin and therefore have a higher chance of being insulin-dependent should *not* be treated with SGLT2 inhibitors. In addition, cats with concurrent illnesses such as hepatic disease, renal disease (International Renal Interest Society stage 3 or higher), pancreatitis, and other serious systemic illness should not be treated with SGLT2 inhibitors. Cats with marked ketosis or DKA are *not* good candidates for treatment with SGLT2 inhibitors due to the risk of inducing or worsening DKA.

Before starting treatment with an SGLT2 inhibitor, a complete history and a physical examination should be performed, including body weight and body condition score. Blood and urine should be collected for a complete blood count, biochemical panel, urinalysis (including urine ketones), fructosamine concentration, total thyroxine concentration, feline pancreatic lipase, and blood or serum β-hydroxybutyrate (BHB)

concentration. Urine dipsticks measure acetoacetic acid and can also be used to measure this ketone in serum or plasma. Measurement of blood or serum BHB is more sensitive than measurement of acetoacetic acid for diagnosis of ketosis. BHB acid can be measured in whole blood by point-of-care meters such as the Precision Xtra meter (Abbott, abbottstore.com), which has been validated in cats, or in serum by a reference laboratory.[7] Abdominal ultrasonography can be helpful to investigate for concurrent pancreatitis in cats with clinical signs of pancreatitis that have an increased feline pancreatic lipase.

MONITORING OF PATIENTS DURING TREATMENT WITH SGLT2 INHIBITORS

Detailed monitoring recommendations for cats treated with SGLT2 inhibitors are shown in TABLE 1. Because the most life-threatening adverse effect of SGLT2 inhibitors is DKA, it is very important to monitor blood and/or urine ketones, especially during the first 2 months of treatment. Cats treated with SGLT2 inhibitors can develop DKA at any time, but in field studies, this complication was most common during the first 2 weeks of treatment.

BOX 2 Reported Adverse Effects of SGLT2 Inhibitors

- Diarrhea
- Vomiting
- Euglycemic diabetic ketoacidosis
- Pancreatitis
- Hepatic lipidosis
- Hypercalcemia
- Hypercholesterolemia
- Hypertriglyceridemia

SGLT2 = sodium–glucose cotransporter 2

ADVERSE EFFECTS OF SGLT2 INHIBITORS IN CATS

The most common side effect of treatment with SGLT2 inhibitors is gastrointestinal upset, resulting in clinical signs such as diarrhea, vomiting, anorexia, and dehydration (BOX 2). The most serious adverse effects reported in cats treated with SGLT2 inhibitors are DKA (which may be euglycemic), pancreatitis, and hepatic lipidosis. Other less common side effects are hypercalcemia, hyperlipidemia, and urinary tract infection.

TABLE 1 Monitoring Recommendations for Cats Treated With SGLT2 Inhibitors

TIME AFTER TREATMENT	MONITORING	ACTION
2–5 days 7–10 days	▪ Physical exam including weight ▪ Urine ketones/blood BHB	▪ **Continue SGLT2 inhibitor** unless BHB is not decreasing, then discontinue drug and transition to insulin. ▪ **Recheck at the 2-week time point**
2 weeks	▪ Physical exam including weight ▪ Urine ketones/blood BHB ▪ Blood glucose/blood glucose curve[a] ▪ Fructosamine	▪ **Continue SGLT2 inhibitor** unless cat is losing weight or if BHB is rising, then discontinue drug and transition to insulin. ▪ If average blood glucose from an 8-hour curve is ≥250 mg/dL and/or serum fructosamine is above reference range, monitor closely. ▪ **Recheck in 2 weeks**
4 weeks	▪ Physical exam including weight ▪ Urine ketones/blood BHB ▪ Blood glucose/blood glucose curve[a] ▪ Fructosamine	▪ **Continue SGLT2 inhibitor** unless cat is losing weight or if BHB is rising, then discontinue drug and transition to insulin. ▪ If average blood glucose from an 8-hour curve is ≥250 mg/dL and/or serum fructosamine is above reference range, monitor closely. ▪ **Recheck in 4 weeks**
8 weeks	▪ Physical exam including weight ▪ Urine ketones/blood BHB ▪ Blood glucose/blood glucose curve[a] ▪ Fructosamine	▪ **Continue SGLT2 inhibitor and recheck every 3 months or earlier if adverse effects develop** ▪ If cat is losing weight or if BHB is rising, then discontinue drug and transition to insulin. ▪ If average blood glucose from an 8-hour curve is ≥250 mg/dL and/or serum fructosamine is above reference range, transition to insulin.

[a]*Required by the U.S. Food and Drug Administration for bexagliflozin but not velagliflozin.*
BHB = β-hydroxybutyrate; SGLT2 = sodium–glucose cotransporter 2.

Gastrointestinal Upset

Diarrhea, likely due to inhibition of the SGLT1 protein in the gastrointestinal tract, is the most common side effect seen with SGLT2 inhibitors in cats. Diarrhea is usually self-limiting, rarely requires cessation of treatment, and usually improves with supportive care. Similarly, transient vomiting, hyporexia, or anorexia can occur. Treatment with SGLT2 inhibitors should be discontinued in cats that become anorexic, depressed, or dehydrated during treatment.

Diabetic Ketoacidosis

DKA is the most serious complication associated with SGLT2 inhibitors and likely occurs due to a complete lack of endogenous insulin secretion from the pancreatic β-cells. DKA is most common within the first 14 days after starting treatment with SGLT2 inhibitors. DKA may also develop at any time during treatment if there is progressive loss of pancreatic β-cells or if concurrent illness causes insulin resistance, anorexia, or other signs of illness. Because of the effects of ongoing SGLT2 inhibition, cats that develop DKA while treated with SGLT2 inhibitors may be euglycemic rather than hyperglycemic.

Euglycemic DKA is a challenge for veterinarians to recognize and treat. Careful monitoring of cats for early clinical signs of ketosis (i.e., lethargy, anorexia, vomiting, weight loss) and frequent measurement of urine ketones and blood or serum BHB are very important to prevent development of fulminant DKA. Treatment of DKA requires cessation of treatment with the SGLT2 inhibitor and initiation of treatment with regular insulin given by either intravenous infusion or intermittent intramuscular injection. In cats that are euglycemic, intravenous dextrose should be administered concurrently to prevent hypoglycemia. Cats with concurrent renal or hepatic disease may have prolongation of metabolism of SGLT2 inhibitors, and therefore euglycemia can persist for longer than expected after cessation of treatment with the SGLT2 inhibitor.

BOX 3 Treatment of Diabetic Ketoacidosis

- Intravenous crystalloid fluid therapy (replacement of dehydration and maintenance)
- Electrolyte supplementation (e.g., potassium, phosphorus)
- Regular insulin administered as continuous-rate infusion or intermittent intramuscular injection
- Dextrose supplementation in fluids to prevent hypoglycemia (2.5% to 7.5%)
- Nutritional support (e.g., appetite stimulants, antiemetics, feeding tube)
- Treatment of other concurrent illness
- Monitoring of acid–base balance, electrolytes, and serum/urine ketones

Treatment with SGLT2 inhibitors should be discontinued in cats that become anorexic, depressed, or dehydrated during treatment.

Pancreatitis

The risk of clinical pancreatitis in cats treated with SGLT2 inhibitors can be decreased by screening for pancreatitis before treatment. Cats should be evaluated for clinical signs of pancreatitis, and the feline pancreatic lipase and/or abdominal ultrasound used to support or refute the diagnosis. In cats that develop clinical signs of pancreatitis during treatment, the SGLT2 inhibitor should be discontinued and the cat should be transitioned to insulin treatment. Additional treatments for pancreatitis may include intravenous fluids, antinausea drugs, appetite stimulants, and nutritional support, depending on the clinical signs.

Hepatic Lipidosis

Hepatic lipidosis is a possible complication of pancreatitis and DKA and likely occurs due to anorexia. Diagnosis relies on documentation of increased liver enzymes and hyperbilirubinemia. Cats with hepatic lipidosis may have prolonged metabolism of SGLT2 inhibitors. Treatment relies on supportive care, nutritional support with a feeding tube, appetite stimulants, and antinausea drugs.

Hypoglycemia

In contrast to treatment with insulin, hypoglycemia is rare in cats treated with SGLT2 inhibitors because the SGLT1 protein in the kidney can resorb up to 40% to 50% of the filtered glucose load. When hypoglycemia occurs, it is typically mild and not associated with clinical signs.

TREATMENT OF CATS WITH ADVERSE EFFECTS DUE TO SGLT2 INHIBITORS

The prognosis for cats with severe adverse effects from SGLT2 inhibitors is best if the disorder is identified as soon as possible. Cats treated with SGLT2 inhibitors should therefore be monitored very carefully during the first 8 weeks of treatment (**TABLE 1**). After the initial 8 weeks of treatment, cats that continue on SGLT2 inhibitors should be reevaluated at least every 3 months or whenever they show signs of systemic illness. In any cat that develops a serious adverse effect associated with treatment with an SGLT2 inhibitor, the drug should be discontinued immediately and the cat transitioned to insulin.

Although cats are most likely to develop adverse effects during the first few weeks of treatment, any cat that develops clinical signs of systemic illness at any point during treatment should be carefully evaluated for complications such as DKA and pancreatitis. It is very important to be aware that the presence of euglycemia does *not* rule out DKA. Therefore, careful screening before treatment and careful monitoring for ketosis during treatment are extremely important. A delay in recognition and treatment of DKA and euglycemic DKA may result in increased morbidity and mortality. Treatment of DKA can be found in **BOX 3**.

SUMMARY

The SGLT2 inhibitors are an exciting new class of drugs in veterinary medicine that are effective for the management of newly diagnosed diabetes mellitus in the majority of newly diagnosed diabetic cats. Both bexagliflozin and velagliflozin cause a rapid decrease in the blood glucose, decrease the fructosamine concentration, and improve clinical signs of diabetes mellitus in most diabetic cats.

The most common side effect of treatment with SGLT2 inhibitors is gastrointestinal upset. Some cats treated with SGLT2 inhibitors develop DKA, which is often euglycemic. If serious adverse effects occur, treatment with the SGLT2 inhibitor should be discontinued immediately and treatment with short-acting insulin, dextrose, and supportive care initiated until the cat can be transitioned to a longer-acting insulin. TVP

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Disclosure

Dr. Scott-Moncrieff has established professional relationships (which include consulting and speaking fees) with Boehringer Ingelheim Animal Health and Elanco Animal Health.

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Dr. Scott-Moncrieff received her veterinary degree from the University of Cambridge in 1985. She completed an internship in small animal medicine and surgery at the University of Saskatchewan, Canada, and a residency and master of science degree in internal medicine at Purdue University. In 1989, she joined the faculty of Purdue University, where she is currently a professor of small animal internal medicine and head of the department of veterinary clinical sciences. She is a diplomate of the ACVIM and the ECVIM. Her research and clinical interests are canine and feline endocrinology, and she is an author of more than 70 peer-reviewed publications.