INSULIN AND ORAL HYPOGLYCEMIC THERAPY
Deborah S Greco DVM, PhD, Diplomate ACVIM
Nestle Purina Petcare

**Oral hypoglycemics**

Indications for oral hypoglycemic therapy in type 2 diabetic cats include normal or increased body weight, lack of ketonuria, no underlying disease (pancreatitis, pancreatic tumor), history of diabetogenic medications, and the owners’ willingness to administer oral medication rather than an injection. Diet should consist of low-carbohydrate/high-protein foods only (preferably canned).

Cats with early type 2 diabetes are most likely to respond to any oral hypoglycemic agent. Sulfonyureas, such as glipizide, increase insulin secretion and improve insulin resistance. Because they provoke insulin release, sulfonylureas may promote progression of pancreatic amyloidosis. In cats, glipizide has been used to successfully treat diabetes mellitus at a dosage of 2.5 mg twice daily when combined with a high-protein, low-carbohydrate diet. The patient is evaluated weekly (urine glucose) or every two-four weeks (fructosamine) for a period of two to four months. Gastrointestinal side effects, which occur in about 15% of cats treated with glipizide, usually resolve when the drug is administered with food. A new sulfonylurea, glimepiride (Amaryl—Aventis Pharmaceuticals) has recently entered the human market; this compound has fewer side effects than glipizide and may be dosed once daily at 2 mg per cat.

Alpha-glucosidase inhibitors impair glucose absorption from the intestine by decreasing fiber digestion and the resulting glucose production from food sources. These medications are not absorbed systemically and may be used in conjunction with other oral hypoglycemics or insulin. Acarbose may be used as the sole initial therapy in obese prediabetic patients suffering from insulin resistance or as adjunct therapy with sulfonylureas or insulin to enhance the hypoglycemic effect in patients with diabetes mellitus. The author has had experience using acarbose at a dosage of 12.5 mg/cat BID administered with a meal. The glucose-lowering effect of acarbose alone is mild with blood glucose concentrations decreasing only into the 250 to 300 mg/dl (14-17 mmol/l) range. However, acarbose is an excellent agent when combined with insulin to improve glycemic control. Side effects are rare with appropriate diet adjustments but, at high dosages, may include flatulence, loose stool, and diarrhea.

**Insulin**

Although all mammalian insulin is structurally similar, small differences in amino acid sequences may be found between species. Mammalian insulin is composed of 51 amino acids arranged in two polypeptide chains. The A-chain contains 21
amino acids and the B chain contains 30 amino acids. Beef insulin is most similar to cat insulin, only differing by one amino acid.\textsuperscript{21} Lente insulin is available as Vetsulin or Caninsulin (Intervet), but Ultralente is no longer available from any company. When contemplating a change in insulin source, consider that different types and brands have different pharmacologic properties. Synthetic insulins, such as Lantus (glargine) and Levamir (Detemir), have been developed for use in human medicine. Preliminary research on glargine suggests that it has some advantages over PZI insulin in cats. In fact, recent studies have shown that a combination of glargine and a low-carbohydrate, high-protein diet resulted in 100% remission of insulin dependence in cats. Detemir insulin has not been investigated for use in cats, but appears to be similar to glargine. Detemir is the insulin of choice in dogs when Lente becomes unavailable; the dose is 0.1-0.2 U/Kg BID.

Initial insulin doses range from 0.2-0.5 U/kg; however, most cats are readily managed on two units twice daily as a starting dose.\textsuperscript{22} If intermediate-acting insulin is used, it must be administered to cats twice daily because of its short duration of action. Glargine (Lantus insulin) should be used cautiously in cats to avoid hypoglycemia. A dose of one to two units twice daily is recommended, along with careful blood or urine monitoring, to avoid hypoglycemic episodes.\textsuperscript{22}

The injection site should be discussed with pet owners, as insulin absorption differs from site to site. In animals, the back of the neck (scruff) is commonly used for insulin injection. However, this site is not recommended because of lack of blood flow and the potential for increased fibrosis caused by repeated injections at this site. Instead, the recommended injection sites are along the lateral abdomen and thorax. The owner should rotate the site of injection daily. Many commercially available pamphlets outline injection techniques, feeding, and hypoglycemic episode management, and provide a log sheet for owners to record food intake, clinical signs, urine glucose measurements, and insulin dosages.

**Monitoring diabetics**

Urine glucose monitoring may be performed at home by owners, is not affected by stress, and may indicate insulin-induced hyperglycemia (Somogyi effect). Urine glucose is a measure of trends in blood glucose and should not be used alone to adjust insulin dosages. However, urine glucose should decrease to trace or one plus with appropriate therapy. Consistently high urine glucose indicates the need for blood glucose evaluation. It is vitally important that the client monitor the urine sugar to determine if and when the cat is ready to go off insulin. This is best accomplished using the Glucotest system, a home urine glucose monitoring system for cats that allows clients to wean their pets off of insulin. The Glucotest packets can be sprinkled in the litter pan over premium clumping litter and checked daily for color change.
Glucose monitors designed for home monitoring in people are inexpensive, accurate, rapid, and require only a drop of blood. Although reasonably accurate in the blood glucose range of 60-120 mg/dl (4-12.5 mmol/L), these monitors are designed to read lower than the actual value as glucose approaches the hypoglycemic range. Such factors as altitude, oxygen therapy, patient hematocrit, shock, dehydration, severe infection, and out-of-date or improperly stored test strips, can all affect the monitors' accuracy. Whole blood glucose concentrations are lower than serum glucose concentrations, so veterinarians should consult the monitor manufacturer to determine suitability for feline patients. A veterinary glucose monitor marketed as the Abbott AlphaTRAK has the highest correlation to clinical laboratory sample glucose analysis. The Bayer Ascensia Contour and the Roche Accu-Chek Advantage are both excellent human monitors, but fall short of the accuracy of the Abbott product when used in animals. Recently, continuous glucose monitors have been developed by Abbott and other companies for remote interstitial glucose monitoring at home or in the veterinary hospital. These small devices are inserted between the shoulder blades and contain a glucose sensor combined with a transmitter device. The receiver and monitor obtain messages from the sensor and display continuous glucose concentrations throughout the day. The monitor may be attached to the animals collar or to a cage. It is very rare to obtain a perfect glucose curve in a single patient. The glucose nadir is the lowest concentration of blood glucose on the curve and should occur approximately halfway through the dosing interval. For example, if insulin is administered every 12 hours, the nadir should fall 5 to 6 hours after the insulin dose.

The time of the glucose nadir indicates the time of peak insulin action, and the ideal blood glucose curve should have a nadir between 100 to 150 mg/dl (5 to 8 mmol/L). The duration of insulin action is related to both the time of the glucose nadir and the absolute concentration of the glucose nadir, in that you cannot determine insulin duration until achieving the target glucose nadir concentration of 80 to 120 mg/dl (4 – 7 mmol/L). If the target glucose nadir is achieved approximately halfway through the dosing interval, the duration of action of insulin and, thus, the type of insulin used, should be adequate. The glucose differential is the difference between the absolute concentration of glucose at the nadir and the absolute concentration of glucose before the next insulin dose. The glucose differential should be less than 150 to 200 mg/dl (8-11 mmol/L) in cats.

Glycosylated blood proteins are indicative of mean glucose concentrations in serum over an extended period of time and may be used to monitor long-term insulin therapy. These proteins are particularly useful in monitoring diabetic cats that may be stressed by hospitalization and serial blood glucose curves. As plasma glucose concentrations increase, glycosylation of hemoglobin and serum proteins increases proportionately. Glycosylation of serum proteins, such as albumin, forms fructosamine. Because albumin has a shorter life span than hemoglobin, fructosamine concentrations reflect more recent changes (one to three weeks) in serum glucose concentrations than glycosylated hemoglobin.
concentrations. Fructosamine concentrations less than 400 to 450 \( \mu \text{mol/L} \) are associated with good to excellent glycemic control; concentrations of 450 to 550 \( \mu \text{mol/L} \) indicate fair to good control; and serum fructosamine greater than 550 \( \mu \text{mol/L} \) indicates poor glycemic control (Figure 2). Relative changes in serum fructosamine may be more helpful than absolute values in some cases.