Insulin glargine treatment of a ferret with diabetes mellitus

Laurie Hess, DVM, DABVP

Case Description—A 7.5-year-old spayed female ferret was evaluated because of weight loss despite a good appetite. Pancreatic insulinoma had been diagnosed at another animal hospital on the basis of detection of low blood glucose concentration on 1 occasion; however, concurrent determination of blood insulin concentration was not performed. The ferret had been treated SC with methylprednisolone acetate (unknown dosage) every 30 days for 2 years. No follow-up data regarding blood glucose concentration were available.

Clinical Findings—On physical examination, the ferret was thin (weight, 0.619 kg [1.36 lb]) and bruised easily. Serum biochemical analysis revealed hyperglycemia (blood glucose concentration, 855 mg/dL; reference range, 63 to 134 mg/dL).

Treatment and Outcome—Glucocorticoid injections were discontinued, and the ferret was administered prednisolone (1.13 mg/kg [0.51 mg/lb], q 12 h for 14 days, then 0.56 mg/kg [0.25 mg/lb], q 12 h for 7 days) orally. After prednisolone administration was discontinued, hyperglycemia and weight loss persisted. The ferret was administered insulin glargine (0.5 U) SC; blood glucose concentration was monitored every 2 hours for 24 hours, at which time the value had decreased to nearly within reference range. The owner continued insulin glargine administration at that dose every 12 hours; after 77 days of treatment, the ferret's weight was 0.731 kg (1.61 lb), which was considered normal, and blood glucose concentration was within reference range.

Clinical Relevance—Regular SC administration of insulin glargine was successful in the treatment of diabetes mellitus in the ferret of this report and may be effective for other diabetic ferrets. (*J Am Vet Med Assoc* 2012;241:1490–1494)

A 7.5-year-old female spayed ferret weighing 0.619 kg (1.36 lb) was evaluated at the Veterinary Center for Birds and Exotics, Bedford Hills, NY, because of weight loss despite a good appetite. A diagnosis of pancreatic insulinoma had been made previously by another veterinarian on the basis of a single measurement of hypoglycemia (determined with a handheld glucometer); that assessment had been performed without concurrent evaluation of blood insulin concentration. The ferret had been treated SC with methylprednisolone acetate (unknown dosage) every 30 days for 2 years; no follow-up data regarding blood glucose concentration had been obtained.

On initial evaluation, the ferret was thin, had muscle wasting, and bruised easily. The owner reported that the ferret was eating well but losing weight and appeared weak. A 0.3-mL sample of blood was collected from a lateral saphenous vein and analyzed within 5 minutes after collection. Serum biochemical analysis, performed with an in-hospital, tabletop serum biochemical analyzer,[a] revealed hyperglycemia (blood glucose concentration, 855 mg/dL; reference range, 63 to 134 mg/dL[1]) and mild azotemia (creatinine concentration, 0.9 mg/dL [reference range, 0.2 to 0.6 mg/dL[1]]; BUN concentration, 45 mg/dL [reference range, 12 to 43 mg/dL[1]]). Results of a CBC, performed with an in-hospital tabletop analyzer,[b] were unremarkable.

From the Veterinary Center for Birds and Exotics, 709 Bedford Rd, Bedford Hills, NY 10507.

The author thanks Melissa Ortiz and Jessica Eisenberg for data collection and input.

Address correspondence to Dr. Hess (lhess@avianexoticsvet.com).

Glucocorticoid injections were discontinued, and treatment with prednisolone sodium phosphate[c] at gradually tapering dosages (1.13 mg/kg [0.51 mg/lb], PO, q 12 h for 14 days, then 0.56 mg/kg [0.25 mg/lb], PO, q 12 h for 7 days) was initiated to wean the ferret slowly off exogenous corticosteroids. One week after commencement of oral prednisolone administration, the ferret remained hyperglycemic (blood glucose concentration, 473 mg/dL) and continued to lose weight (weight, 585 g [1.28 lb]). It had been hoped that the hyperglycemia would be transient and would resolve after the oral prednisolone administration was discontinued. However, 2 weeks later (when oral prednisolone administration was discontinued completely [ie, 3 weeks after the initial evaluation]), the ferret appeared clinically stronger and continued to eat well but remained hyperglycemic (blood glucose concentration, 535 mg/dL).

After discontinuation of oral administration of prednisolone, measurement of blood glucose concentration during a 24-hour period was planned. However, the owner lived some distance from the hospital and was unable to return the ferret for assessment until 3 weeks later (ie, 6 weeks after its initial evaluation). At this point, a 24-gauge IV catheter was placed in the right cephalic vein for blood sample collections. A baseline blood sample (0.3 mL) was analyzed within 5 minutes after collection with the same in-hospital, tabletop serum biochemical analyzer used previously; analysis revealed that the ferret was hyperglycemic (blood glucose concentration, 840 mg/dL). Insulin glargine[d] (0.5 U [measured in a U-100 syringe[e] marked in

0.5-U increments) was administered SC between the ferret's scapulae, and a 0.3-mL blood sample was collected with the catheter every 2 hours for 12 hours by the same person, who processed each sample through the same serum biochemical analyzer within 5 minutes after sample collection. Fourteen hours after the first injection, a second dose of insulin glargine (0.5 U, SC) was administered between the scapulae by the same individual who administered the first dose. A 0.3-mL blood sample was collected for analysis via the catheter every 2 hours for an additional 18 hours (**Figure 1**). During the entire assessment period, the ferret was confined to a small cage and had access to both dry ferret kibble and a high-protein liquid food formulated for syringe feeding to carnivorous animals. The ferret grazed on food and slept intermittently during the assessment.

After completion of 22 hours of the blood glucose concentration assessment, the ferret's blood glucose began to rise dramatically; thus, the ferret was administered an additional dose of insulin glargine (0.5 U, SC) between the scapulae. Additional blood samples were then collected every 2 hours for a total of 32 hours. The ferret was then discharged from the hospital and returned to the care of the owner, who was instructed to administer the insulin at the same dosage and in the same manner as it had been given thus far. The owner also was instructed to monitor the glucose concentration in urine voided in the ferret's paper-lined litter box with commercially available urine dipsticks[f] as often as possible and to continue to administer insulin glargine (0.5 U, SC, q 12 h) if the dipstick test revealed greater than trace amounts (5.5 mmol/L) of glucose in the urine.

The owner continued administration of insulin glargine (0.5 U, SC, q 12 h) between the scapulae for an additional 18 days; during that period, the glucose concentration of the ferret's urine was assessed by use of urine dipsticks at least twice daily, at 12-hour intervals whenever possible, before the next dose of insulin glargine was administered. Results of the dipstick assessment revealed that the ferret's urine was never completely glucose free; on most occasions, the urine was moderately positive (14 mmol/L) for glucose. To reduce the likelihood that the ferret would become hypoglycemic after the owner administered insulin and had to leave for work, the owner ensured that the ferret consumed a meal within minutes after receiving the injection.

Eighteen days after the initial administration of insulin glargine during the first blood glucose concentration curve, the ferret was returned to the hospital. It was eating well, was active, and had gained weight (weight, 0.649 kg [1.43 lb]). A 24-gauge catheter was placed in the left cephalic vein, and a 0.3-mL blood sample was collected via the catheter every 2 hours for 8 hours by the same individual who had performed the previous blood glucose assessment. The owner had administered insulin glargine (0.5 U, SC) between the scapulae approximately 2.5 hours before the first blood sample was collected. The initial blood sample and 4 additional 0.3-mL samples were analyzed with the same in-hospital biochemical analyzer as before; data were used to generate a second (abbreviated) blood glucose concentration curve (Figure 1). During this 8-hour assessment, the ferret was similarly confined to a small cage and had access to both dry ferret kibble and a high-protein liquid food formulated for syringe feeding to carnivorous animals.

The ferret was discharged from the hospital and returned to the care of its owner, who continued administering insulin glargine (0.5 U, SC, q 12 h) between the scapulae when the dipstick assessments revealed greater than trace amounts of glucose in the urine. The ferret continued to eat well and gain weight, and after an additional 2 weeks of insulin glargine treatment, the owner less frequently documented that the ferret's urine was moderately positive for glucose.

Eighty-four days after the initial evaluation and 42 days after the initial administration of insulin glargine, the ferret was reevaluated at the hospital. Its weight was 0.695 kg (1.53 lb). A blood sample was collected approximately 4 hours after the ferret had received the morning dose of insulin glargine; analysis performed in the same manner and with the same in-house serum biochemical analyzer used previously revealed the ferret's blood glucose concentration was within reference range (82 mg/dL).

One hundred nineteen days after the initial evaluation and 77 days after the initial administration of insulin glargine, the ferret had gained weight (weight, 0.731 kg [1.61 lb]) and its blood glucose concentration was at the low end of the reference range (67 mg/dL). The owner reported the ferret was more active and energetic than ever before and that no glucose was detected in the ferret's urine with the dipsticks, even up to 72 hours after administration of a dose of insulin glargine. The owner continued to monitor urine glucose concentration with urine dipsticks at least twice a day (at approx 12-hour intervals). However,

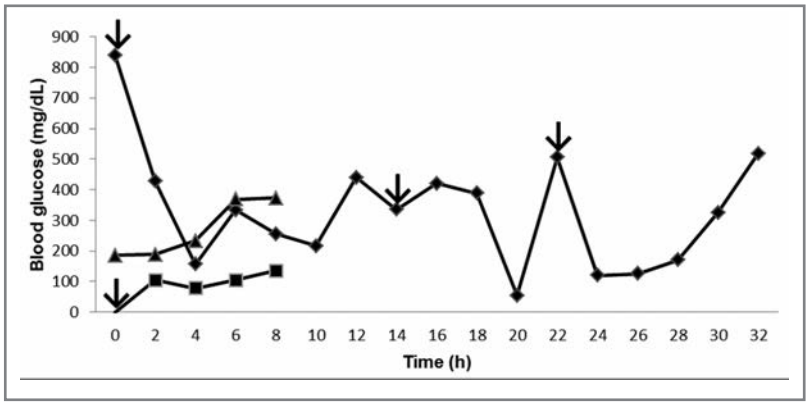

Figure 1—Blood glucose concentrations monitored on 3 occasions in a ferret with diabetes mellitus that was receiving treatment with insulin glargine. The first curve was generated from data obtained at 2-hour intervals for 32 hours after the initial administration of 0.5 U of insulin glargine, SC (diamonds); a second dose was administered at the 14-hour time point; and a third dose was administered at the 22-hour time point. Eighteen days later, another curve was generated from data obtained at 2-hour intervals for 8 hours (squares); the owner had administered 0.5 U of insulin glargine, SC, 2.5 hours before the assessments commenced. One hundred days after the first insulin glargine injection, a third curve was generated from data obtained at 2-hour intervals for 8 hours (triangles); during this third assessment, the ferret had not received insulin glargine (0.5 U, SC) for 72 hours, and the blood glucose concentration remained within reference range until the 6-hour time point. Arrows represent time points at which an insulin glargine injection was administered.

because the dipstick readings revealed no glucose in the urine more frequently than they had previously, the owner no longer administered insulin glargine every 12 hours but rather whenever the dipstick reading was greater than trace amounts (5.5 mmol/L) of glucose in the urine.

The ferret was returned to the hospital 100 days after the initiation of insulin glargine treatment. The ferret was doing well clinically and weighed 0.8 kg (1.76 lb). A 24-gauge catheter was placed in the right cephalic vein, and a 0.3-mL blood sample was collected with the catheter every 2 hours for 8 hours by the same individual who had performed the previous blood glucose assessment. The initial blood sample and 4 additional 0.3-mL samples were analyzed in the same in-hospital chemistry analyzer as before; data were used to generate a third (abbreviated) blood glucose concentration curve (Figure 1). When this third assessment was begun, the ferret had not received any insulin for 72 hours and the owner had recorded negative dipstick test results for glucose in the ferret's urine for 3 consecutive days. During this assessment, blood glucose concentration remained < 200 mg/dL, without any further administration of insulin glargine, for 4 hours (76 hours since the previous insulin glargine injection). At the 4-hour point, the blood glucose concentration increased to > 200 mg/dL. The ferret was discharged from the hospital and returned to the owner's care, who continued to use daily dipstick measurements of glucose in the ferret's urine to determine the need for administration of insulin glargine. At last follow-up, nearly 12 months after the initial administration of insulin glargine, the owner reported that the ferret continued to thrive and was receiving 0.5 U of insulin glargine, SC, every 1 to 3 days.

Discussion

Spontaneous diabetes mellitus is uncommonly diagnosed in ferrets.[2–6] Clinical signs of diabetes mellitus in ferrets are similar to those in other species: lethargy, weight loss despite a good appetite, polyuria, and polydypsia.[4,5,7,8] Hind limb weakness and ataxia may be noticeable if diabetic neuropathy develops.[6] A diagnosis is made on the basis of the presence of compatible clinical signs and documentation of persistent hyperglycemia (blood glucose concentration > 400 mg/dL). In some diabetic ferrets, blood glucose concentrations may persistently exceed 1,000 mg/dL.[4] For ferrets with diabetes mellitus, results of a CBC and blood biochemical analysis may be within reference ranges unless the ferret has ketoacidosis and resultant metabolic changes (eg, acid-base imbalance, hyponatremia, and hyperkalemia) or concurrent infection (eg, cystitis or nephritis).[4] Results of urinalysis may be within reference ranges or may indicate glucosuria, ketonuria, or the presence of bacteria and WBCs with concurrent urinary tract infection.[4,7] To date, the author is unaware of any studies that have determined the renal threshold for glucose in ferrets. Thus, the level of hyperglycemia that exceeds the reabsorption capacity of the proximal renal tubules in ferrets is unknown.

Diabetes mellitus in a 6-year-old black-footed ferret with polyuria, polydipsia, polyphagia, dehydration, weight loss, and marked hyperglycemia has been reported.[9] A diagnosis of diabetes mellitus was made on the basis of the resolution of hyperglycemia following treatment with neutral protamine Hagedorn insulin, although histologic examination of a pancreatic biopsy specimen revealed a sufficient number of insulin-producing beta cells. Diabetes mellitus in that ferret was hypothesized to be the result of decreased release of insulin or resistance to its effects.

Diabetes mellitus was also diagnosed in a 2-year-old ferret with hyperglycemia and ketoacidosis.[10] The ferret was lethargic, dehydrated, twitching, and emaciated with hind limb paresis; it had been fed sugary cereal for over a year. Despite treatment with regular insulin, the ferret died. At necropsy, histopathologic changes in the pancreas were characteristic of diabetes mellitus in other species; there were an appropriate number of pancreatic beta cells, but the cells were diffusely vacuolated and contained both insulin and glycogen. Repeated ingestion of sugar by this ferret was thought to have resulted in chronic hyperglycemia, impaired insulin secretion by beta cells, and peripheral insulin resistance by downregulation of glucose transport systems.

In another report,[3] diagnoses of diabetes mellitus and adrenal gland neoplasia were made for a 6-year-old castrated male ferret with polyuria, polydipsia, weight loss, alopecia, severe hyperglycemia, and high blood sex steroid hormone concentrations. This ferret initially improved during treatment with porcine Lente insulin and leuprolide acetate but eventually developed ketoacidosis and was euthanized. Necropsy revealed chronic active pancreatitis with a marked decrease in pancreatic beta cells, in addition to left adrenocortical carcinoma and right adrenocortical hyperplasia. This appears to have been the first reported case of diabetes mellitus associated with chronic pancreatitis and adrenal neoplasia in a ferret.

Reports[4,6,7,11,12] of iatrogenic diabetes mellitus in ferrets both as a result of treatment with megestrol acetate hormone and following aggressive surgical removal of pancreatic insulinomas (commonly found in domestic ferrets) have been published. Some ferrets that develop diabetes mellitus following partial pancreatectomy for removal of insulinomas develop signs of depression and die within 48 hours after surgery. Most ferrets that are hyperglycemic after insulinoma resection are only transiently affected and do not require long-term insulin treatment; blood glucose concentration usually returns to within reference limits after 1 to 2 weeks.[13] In a few cases, blood glucose concentration normalizes for 4 to 6 weeks.[2] It is theorized that in postoperative diabetic ferrets, transient hyperglycemia is due to residual tumor-derived insulin suppression of islet cells following tumor removal.

Care must be taken not to make a diagnosis of diabetes mellitus for transiently stressed ferrets with blood glucose concentrations that exceed the reference range, but are < 400 mg/dL in the absence of other clinical signs.[11] Transient hyperglycemia with a blood glucose concentration as high as 400 mg/dL has been detected as a 1-time, nonrepeatable event in stressed, clinically normal ferrets; thus, care should be take not to diagnose

diabetes mellitus on the basis of a single blood glucose concentration.[11] In the absence of clinical signs, ferrets with a blood glucose concentration < 400 mg/dL should undergo serial assessments of blood glucose concentration to determine whether hyperglycemia persists and a diagnosis of diabetes mellitus can therefore be made. Chronic stress can lead to excess endogenous corticosteroid release; endogenous corticosteroids or chronic treatment with exogenous corticosteroids increases gluconeogenesis and glycogenolysis, leading to chronic hyperglycemia and resultant increased blood insulin concentrations that can ultimately downregulate insulin receptors, thereby causing subsequent insulin resistance and the development of diabetes mellitus.[5,14] In addition, long-term consumption of high-sugar diets may lead to chronic hyperglycemia that in turn impairs beta-cell function and decreases insulin release, ultimately leading to development of diabetes.[10,14]

Documentation of low blood insulin concentration concurrently with hyperglycemia helps confirm a diagnosis of diabetes mellitus, and insulin assays validated for ferrets are commercially available.[4] High blood insulin concentration in the face of hypoglycemia in ferrets is used to confirm the presence of a pancreatic insulinoma. Hypoglycemia and high blood insulin concentration in a ferret strongly suggest the presence of insulinoma; however, before oral administration of prednisone (typically used to treat insulinomas in ferrets when surgical tumor removal is not attempted) is begun, serial measurements of blood glucose concentration (to document ongoing hypoglycemia) should be undertaken. In addition, if prednisone is administered to treat insulinoma, serial assessments of blood glucose concentration should be performed approximately 7 to 10 days after prednisone treatment is begun until normoglycemia is achieved; blood glucose concentration should be monitored every few months thereafter as the tumor burden grows and resultant insulin output increases.

Detection of a blood insulin concentration that is high or within reference range in the face of hyperglycemia cannot rule out diabetes mellitus; rather, it may indicate insulin resistance or the presence of glucagonoma.[6] To the author's knowledge, there are no commercially available tests to measure circulating glucagon in ferrets, and although histologic evidence of glucagonomas in ferrets undergoing necropsy has been obtained,[5] there are no reports of glucagon-secreting tumors in living ferrets. In diabetic people, cats, and dogs, blood fructosamine and glycosylated hemoglobin concentrations are used to monitor persistent hyperglycemia; however, these tests have not yet been validated in ferrets.[6]

Once a diagnosis of diabetes mellitus has been made, insulin treatment of the ferret is typically initiated to normalize blood glucose concentration.[6] However, few successful treatment protocols for ferrets have been described, and in general, ferrets with diabetes mellitus have a poor prognosis.[5,6,10–13,15] Traditionally, diabetic ferrets have been managed as if they were insulin-dependent diabetic cats, with high-protein, low-carbohydrate ferret or feline diets made accessible to the ferret at all times and with once- to twice-daily SC administration of small empirical doses of regular crystalline insulin, neutral protamine Hagedorn insulin, or ultralente insulin.[9–11] One published protocol for the treatment of diabetes mellitus in ferrets involves SC injection of 0.1 U of neutral protamine Hagedorn insulin every 12 hours or 0.1 U of ultralente insulin every 24 hours.[5] In hospitalized diabetic ferrets, serial blood glucose concentrations are monitored to try to maintain blood glucose concentration between 125 and 200 mg/dL; owners are instructed to continue insulin administration at home on the basis of the results of daily urine dipstick assessments to detect the presence of urinary glucose and ketones. In general, owners are told that urinary glucose concentrations of 5.5 to 14 mmol/L (measured with urine dipsticks) do not necessitate insulin administration to avoid development of hypoglycemia following treatment.[5] An alternate method for monitoring ferrets' blood glucose concentrations at home is the use of lancets (designed for diabetic humans) on ferrets' footpads to obtain small blood samples for glucose determination via a handheld glucometer. However, these glucometers have not been validated for use in ferrets, and in the author's experience, measurements of glucose concentration in a given blood sample determined by use of different portable glucometers can vary widely.

Regardless of the insulin type administered, ferrets with spontaneous diabetes mellitus or those that develop diabetes long after surgical removal of pancreatic insulinomas often have oscillations between hyperglycemia and hypoglycemia and their blood glucose concentration is extremely difficult to regulate. Some do not respond to insulin administration at all, and most ultimately deteriorate clinically and die despite attempted treatment.[5] Ferrets that develop diabetes mellitus transiently immediately following partial pancreatectomy to remove insulinomas have been treated successfully; as hyperglycemia resolves (typically within 1 to 6 weeks after surgery), insulin treatment, if necessary at all, can be discontinued.[2,5,13]

Recently, a synthetic insulin analogue commonly used in humans, insulin glargine, has been used successfully to treat diabetes mellitus in cats and dogs.[6] Insulin glargine has a longer duration of action and lack of peak effect, compared with ultralente insulin or neutral protamine Hagedorn insulin. In diabetic cats, treatment with insulin glargine results in better glycemic control and ultimately a greater chance for diabetic remission than do treatments with other types of insulin. For diabetic people, insulin glargine is marketed as a once-daily injection. In diabetic cats and dogs, insulin glargine has been effective when administered once to twice daily.[16,17]

Spontaneous diabetes mellitus is uncommon in ferrets. The cause of diabetes in the ferret of this report was unknown. However, the ferret received monthly injections of an unknown dosage of methylprednisolone acetate, a glucocorticoid, for 2 years without further determinations of blood glucose concentration. Chronic administration of corticosteroids increases gluconeogenesis and glycogenolysis; in this ferret, resultant hyperglycemia and likely subsequent increased blood insulin concentration as a consequence of long-term

corticosteroid treatment may have led to downregulation of insulin receptors and to insulin resistance, perpetuating hyperglycemia. Beta cells that were secreting high concentrations of insulin may have ultimately stopped producing insulin, resulting in progression of this ferret's condition to insulin-dependent diabetes mellitus.[14]

In hindsight, it would have been prudent to have determined the ferret's blood insulin concentration at the initial evaluation at the Veterinary Center for Birds and Exotics when the ferret was severely hyperglycemic, following the 2-year treatment elsewhere with SC methylprednisolone acetate. If the blood insulin concentration had been low with concomitant severe hyperglycemia, this finding would have supported the hypothesis that this ferret's pancreas was not producing insulin or that the ferret had become resistant to the insulin that was secreted.

To the author's knowledge, no other reports regarding the use of insulin glargine to treat diabetic ferrets have been published. Other attempts at treating ferrets with diabetes mellitus with other forms of insulin have been unsuccessful over the long term. Further studies of insulin glargine's duration of action in diabetic ferrets need to be undertaken; however, initial data from the ferret of this report have indicated that insulin glargine must be administered twice daily to maintain normoglycemia in diabetic ferrets that may require the drug more frequently owing to their smaller sizes and faster metabolic rates, compared with cats and dogs.

As illustrated by the case of this report, insulin glargine offers owners of diabetic ferrets a feasible means of treatment at home, provided they can monitor their ferrets' urine twice daily for the presence of glucose. Owners administering insulin glargine at home to diabetic ferrets must be thoroughly educated regarding the interpretation of urine glucose concentration determinations and about the risks of hypoglycemia. In addition, given the minute amount of insulin glargine to which the ferret of the present report reacted, ferret owners administering insulin glargine at home must use U-100 syringes marked in 0.5-U increments so that potential error in over- and underdosing insulin is minimized.

Whether the ferret of the present report will remain diabetic for the rest of its life is uncertain. At 100 days after the initial administration of insulin glargine (Figure 1), the ferret was normoglycemic for many hours a day after receiving no insulin for > 72 hours, and it only required insulin glargine (0.5 U, SC, q 1 to 3 d) to maintain blood glucose concentration below the target high value of 200 mg/dL. Considering that the owner used urine dipstick measurements to direct insulin treatment and administered insulin only when the dipstick assessments revealed that glucose was present in the urine in greater than trace amounts, it is possible that this ferret's blood glucose concentration was actually > 200 mg/dL but that this was not reflected in urine glucose readings. To the author's knowledge, no studies have been performed to date to correlate blood glucose concentrations with urine dipstick measurements in ferrets.

For the ferret of this report, insulin glargine administration appeared to successfully control the blood glucose concentration, and the management plan was to generate follow-up blood glucose concentration curves at 1-month intervals to track the progression of the disease and to determine whether its insulin requirements were changing. Insulin glargine administration should be considered for the treatment of diabetic ferrets by owners at home.

a. VetScan VS2, Abaxis, Union City, Calif.
b. VetScan HM5, Abaxis, Union City, Calif.
c. Hi-Tech Pharmacal Inc, Amityville, NY.
d. Lantus, Sanofi-aventis US, Bridgewater, NJ.
e. U-100 insulin syringes (30 gauge, 3/8 inch, 3/10 mL), CVS Pharmacy Inc, Woonsocket, RI.
f. Clinistix, Bayer Corp, Elkhart, Ind.

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