Detemir insulin for the treatment of diabetes mellitus in dogs

Federico Fracassi, DVM, PhD; Sara Corradini, DVM; Michaela Hafner, DVM; Felicitas S. Boretti, DVM; Nadia S. Sieber-Ruckstuhl, DVM; Claudia E. Reusch, DVM

Objective—To investigate the effects of insulin detemir in dogs with diabetes mellitus.

Design—Prospective, uncontrolled clinical trial.

Animals—10 client-owned dogs with naturally occurring diabetes mellitus.

Procedures—Dogs were treated with insulin detemir SC every 12 hours for 6 months. Follow-up evaluations were done at 1, 2, 4, 12, and 24 weeks and included evaluation of clinical signs and measurement of blood glucose concentration curves and serum fructosamine concentrations.

Results—Insulin detemir administration resulted in a significant decrease in blood glucose and serum fructosamine concentrations at 6 months, compared with pretreatment values. Median insulin dosage at the end of the study was 0.12 U/kg (0.055 U/lb; range, 0.05 to 0.34 U/kg [0.023 to 0.156 U/lb], SC, q 12 h). Hypoglycemia was identified in 22% (10/45) of the blood glucose concentration curves, and 6 episodes of clinical hypoglycemia in 4 dogs were recorded. A subjective improvement in clinical signs was observed in all dogs during the 6-month study period. On the basis of clinical signs and blood glucose concentration curves, efficacy of insulin detemir at the end of the study was considered good in 5 dogs, moderate in 3, and poor in 2.

Conclusions and Clinical Relevance—Results suggested that SC injection of insulin detemir every 12 hours may be a viable treatment for diabetes mellitus in dogs. Insulin detemir dosages were lower than reported dosages of other insulin types needed to maintain glycemic control, suggesting that insulin detemir should be used with caution, especially in small dogs. (J Am Vet Med Assoc 2015;246:73–78)

Diabetes mellitus occurs commonly in dogs and is controlled with daily insulin administration. Insulin types commonly used for treatment of diabetes mellitus in dogs include porcine insulin zinc suspension, recombinant human NPH insulin, recombinant human protamine zinc insulin, and insulin glargine.

Insulin analogs are modified forms of insulin that differ from native insulin but have the same physiologic effect. Insulin glargine and insulin detemir are synthetic long-acting insulin analogs designed to maintain a basal concentration of insulin in humans with diabetes mellitus. Insulin analogs have revolutionized the management of diabetes mellitus in human medicine and have become potential choices for the treatment of diabetes mellitus in dogs and cats. Insulin glargine forms microprecipitates in the subcutaneous tissues, which results in slow absorption and a long duration of action in humans, dogs, and cats. Insulin glargine is considered by some to be the insulin of choice for the treatment of diabetes mellitus in cats, and 1 study showed that the remission rate of diabetes mellitus was higher in cats treated with insulin glargine than in cats treated with other types of insulin.

Insulin detemir differs from human insulin in that the threonine in position B30 of the primary amino acid sequence of the polypeptide chain has been removed and the ε-amino group of the lysine in position B29 has been acylated with a 14-carbon myristoyl fatty acid. The fatty acid modification permits insulin detemir to reversibly bind to albumin, which slows absorption and provides a prolonged and consistent metabolic effect for up to 24 hours in humans. A pharmacodynamic study that involved 3 clinically normal dogs, 3 dogs in which diabetes mellitus was experimentally induced with streptozotocin, and 2 dogs with juvenile-onset diabetes mellitus revealed that insulin detemir has a greater potency than do other insulin types and, as a result, should be used at lower dosages.

Little is known about the use of insulin detemir for the management of diabetes mellitus in dogs. Therefore, the aim of the study reported here was to assess the efficacy and safety of insulin detemir in client-owned dogs with diabetes mellitus.

Materials and Methods

Inclusion criteria—Client-owned dogs with newly diagnosed or poorly regulated diabetes mellitus were
enrolled in the study. The diagnosis of diabetes mellitus was made on the basis of typical clinical signs, blood glucose concentration > 200 mg/dL after food had been withheld for at least 10 hours, glucosuria, and serum fructosamine concentration > 340 µmol/L. At the time of enrollment, dogs were considered to have poorly regulated diabetes mellitus if they had polyuria, polydipsia, polyphagia, or weight loss in addition to blood glucose concentrations > 200 mg/dL throughout a 10-hour period despite treatment with insulin at a dosage ≥ 0.5 U/kg (0.23 U/lb), SC, every 12 hours. To identify any concurrent disorders, a CBC, serum biochemical profile, urinalysis, aerobic bacterial culture of a urine sample obtained by means of cystocentesis, and abdominal ultrasonography were performed in all dogs at the time of study enrollment. Additional testing such as the low-dose dexamethasone suppression test, assessment of thyroid function, or measurement of canine pancreatic lipase immunoreactivity was done if clinically indicated. Dogs with severe concurrent disease (eg, hyperadrenocorticism, hypothyroidism, renal disease, or neoplasia) and dogs that had been treated with progestogens or glucocorticoids in the previous 2 months were excluded from the study.

Dogs with acute pancreatitis were included only after all clinical signs of acute pancreatitis had resolved. Dogs with diabetic ketoacidosis were included in the study after they had been stabilized with intensive treatment, which included administration of regular crystalline insulin. Dogs with a lower urinary tract infection were included in the study if the infection resolved after a single course of antimicrobials. Owners did not receive financial compensation to participate in the study. The study protocol was approved by the Scientific Ethics Committee of the University of Bologna, Italy.

**Study design**—The study was designed as a prospective, uncontrolled, 6-month clinical trial. Before treatment (day 0), a history was obtained, dogs were weighed, a physical examination was performed, and a CBC, serum biochemical profile (which included measurement of serum fructosamine concentration), urinalysis, and bacteriologic culture of a urine sample were performed. Insulin detemir was administered to all dogs (starting dosage, 0.02 to 0.13 U/kg [0.009 to 0.059 U/lb], SC, q 12 h). To avoid errors in administration of very small amounts of insulin, a diluent was used in 1 dog weighing < 5 kg (11.0 lb). A diet low in simple carbohydrates and high in fiber was recommended for all dogs, but owners, in agreement with their attending veterinarian, were permitted to change the diet to ensure that dogs ate consistently. Dogs received a balanced and complete diet every 12 hours at the time of insulin administration. Follow-up evaluations were performed 1, 2, 4, 12, and 24 weeks after the initial evaluation and included an assessment of clinical signs and determination of serum fructosamine concentration and blood glucose concentration curves. For blood glucose concentration curves, food and insulin were typically administered in the clinic, and glucose concentrations were measured before and 2, 4, 6, 8, and 10 hours after insulin injection. For dogs that were unwilling to eat in the clinic, food and insulin were given at home and blood glucose concentrations were measured after the dog arrived at the clinic (< 2 hours after insulin administration). The insulin dosage was adjusted in increments of 0.5 to 1.0 U/dog at each evaluation as required; the aim was to maintain blood glucose concentrations between 90 and 270 mg/dL. Insulin dosage adjustments were made by the attending veterinarian and were based on the owner’s perception of clinical signs in response to treatment (including evidence of hypoglycemic episodes, body weight, and physical examination results), blood glucose concentration curve, and serum fructosamine concentration. Mild hypoglycemia was defined as blood glucose concentration between 60 and 89 mg/dL, and severe hypoglycemia was defined as a blood glucose concentration < 60 mg/dL.

**Analytic methods**—Blood glucose concentrations were measured in capillary blood obtained from the inner surface of the pinna with a handheld glucometer validated for use in dogs. Sampling of capillary blood was done with a lancing device as described. Samples for CBCs, serum biochemical analyses, and urinalyses were analyzed by means of standard laboratory methods. Fructosamine concentrations were measured with a commercial analyzer and commercial reagent.

**Assessment of insulin detemir efficacy**—Biochemical variables used to assess glycemic control of diabetes mellitus included blood glucose concentration curve nadir, median blood glucose concentration for the blood glucose concentration curve, and serum fructosamine concentration. A blood glucose concentration curve nadir of 90 to 180 mg/dL was considered ideal. An optimal blood glucose concentration curve was one that had > 50% of the blood glucose concentrations in the range of 90 to 270 mg/dL. Glycemic control was considered good, moderate, or poor for median blood glucose concentrations for the blood glucose concentration curves < 234 mg/dL, 234 to 306 mg/dL, and > 306 mg/dL, respectively. Glycemic control was considered good, moderate, or poor for serum fructosamine concentrations < 450 µmol/L, 450 to 550 µmol/L, and > 550 µmol/L, respectively. Glycemic control was considered good, moderate, or poor on the basis of the owner’s observations if polyuria and polydipsia were reported as absent, present but improved, or present and unchanged, respectively.

Insulin detemir efficacy was also classified as good, moderate, or poor on the basis of clinical parameters, including body weight stability (ie, < 5% fluctuation in body weight), results of physical examinations, and assessments of glycemic control. Efficacy was classified as good when body weight was stable or increasing, the veterinarian believed the dog was active with normal mental status and without obvious signs of dehydration, and glycemic control was good. Efficacy was classified as moderate when body weight was stable or increasing, the veterinarian believed the dog was active with normal mental status and without obvious signs of dehydration, and glycemic control was moderate or poor. Efficacy was classified as poor when the veterinarian believed the dog was apathetic, the dog had asthenia or dehydration (> 6%) or was losing weight (> 5%), and glycemic control was moderate or poor.
Data analysis—All variables were reported as medians and ranges. Differences were tested by means of the Wilcoxon matched pairs test. All analyses were performed with the aid of commercially available software. Values of $P < 0.05$ were considered significant.

Results

Animals and results at the time of enrollment—Ten dogs with diabetes mellitus met the inclusion criteria and were enrolled in the study. Median age was 9 years (range, 6 to 13 years). Five of the 10 dogs were spayed females, 3 were sexually intact females, 1 was a neutered male, and 1 was a sexually intact male. All 3 sexually intact female dogs were spayed within 20 days after inclusion in the trial. Median body weight was 9.6 kg (21.1 lb; range, 3.7 to 42 kg [8.1 to 92.4 lb]), and median body condition score (on a scale from 1 to 9) was 5 (range, 4 to 7). There were 3 English Setters, 2 mixed-breed dogs, 1 Cairn Terrier, 1 Shih Tzu, 1 Rottweiler, 1 Jack Russell Terrier, and 1 Poodle. Six of the 10 dogs had newly diagnosed diabetes mellitus; the remaining 4 (3 spayed females and 1 neutered male) had poorly regulated diabetes mellitus despite treatment with porcine insulin for a median of 5 months (range, 2 to 8 months). One dog with newly diagnosed diabetes mellitus had a urinary tract infection that was successfully treated with antimicrobials. Two dogs were enrolled after resolution of diabetic ketoacidosis, and 1 dog was enrolled after resolution of acute pancreatitis. All dogs had markedly increased blood glucose concentrations and increased fructosamine concentration at the time of study enrollment (Table 1). Dogs were fed a variety of diets, including commercial dry and home-cooked diets (3), commercial dry and canned diets (2), high-fiber dry diets (2), a low-fat canned diet (1), a commercial dry diet with bones and raw food (1), and a home-cooked diet (1).

Outcome—All 10 dogs completed the 6-month trial period. Median insulin dosage at the time of study enrollment was 0.11 U/kg (0.05 U/lb; range, 0.02 to 0.13 U/kg [0.009 to 0.059 U/lb]), SC, every 12 hours. During the study period, the insulin dosage was increased in 7 dogs, decreased in 2, and not adjusted in 1. Of the 9 dogs in which the insulin dosage was adjusted, 2 had a single dosage adjustment, 6 had 2 to 3 dosage adjustments, and 1 had 4 dosage adjustments. Median insulin dosage at the end of the study (0.12 U/kg [0.055 U/lb]; range, 0.05 to 0.34 U/kg [0.023 to 0.155 U/lb], SC, q 12 h) was significantly higher than initial insulin dosage (Table 1). A subjective improvement in clinical signs was observed in all dogs during the study period. Polyuria and polydipsia were observed in 8 dogs at the time of enrollment and in 5 dogs after 6 months of treatment. Body weight did not change after 6 months of treatment. Cataracts were present in 4 dogs at the time of enrollment and in 5 dogs after 6 months of treatment. In 1 dog, cataracts developed after 4 weeks of treatment with insulin detemir.

Blood glucose concentration curve nadirs, median blood glucose concentration for the blood glucose concentration curves, and serum fructosamine concentrations before and 1, 2, 4, 12, and 24 weeks after initiation of insulin detemir treatment were summarized (Table 1). Median glucose concentrations for the blood glucose concentration curve were significantly lower at weeks 1, 2, and 24 than they were prior to the initiation of insulin detemir treatment (Figure 1). At the end of the study, blood glucose concentration curves were classified as optimal in 5 of the 10 dogs. Overall, 20 of the 45 (44%) blood glucose concentration curves were classified as optimal. On the basis of median blood glucose concentration for the blood glucose concentration curves at the end of the study, glycemic control was classified as good in 3 dogs, moderate in 4, and poor in 3.

The time when the blood glucose concentration nadir occurred varied from 0 to 10 hours after insulin detemir administration. When all 45 blood glucose concentration curves were considered, the nadir most commonly occurred 4 (n = 10 [22%]), 6 (12 [27%]), or 8 (11 [25%]) hours after insulin administration (Figure 2). Serum fructosamine concentrations were significantly ($P = 0.006$) decreased after 6 months of treatment with insulin detemir, compared with concentrations at the time of enrollment. On the basis of serum fructosamine concentration measured at the end of the study, glycemic control was classified as good in 4 dogs, moderate in 4, and poor in 2. On the basis of the owners’ observations, glycemic control at the end of the study was considered good in 7 dogs and moderate in 3.

On the basis of clinical parameters (ie, body weight stability, results of physical examination, and assessments of glycemic control), efficacy of insulin detemir...
at the end of the study was classified as good in 5 dogs, moderate in 3, and poor in 2.

Adverse effects and hypoglycemia—No adverse reactions were seen at the sites of insulin detemir injection. Mild or severe hypoglycemia (blood glucose concentration \(\leq 89 \text{ mg/dL}\)) was a frequent problem and occurred in 6 dogs (10/45 [22%] total blood glucose concentration curves). Six episodes of hypoglycemia characterized by lethargy, weakness, and abnormal gait were reported by the owners of 4 dogs; only 2 of these episodes (1 dog each) were confirmed by measurement of blood glucose concentration. These 2 episodes occurred 2 and 4 months after initiation of insulin detemir treatment. One of the 2 dogs had stupor and was admitted to the clinic in lateral recumbency; the other dog reportedly was falling down. Blood glucose concentration was < 20 mg/dL in both dogs, and clinical signs resolved with IV administration of dextrose-containing fluids. All 4 dogs that developed clinical signs most likely attributable to hypoglycemia had a body weight < 11 kg (24.2 lb; median, 8.5 kg [18.7 lb]; range, 7.5 to 10.9 kg [16.5 to 24.0 lb]).

Discussion

In the present study, administration of insulin detemir SC every 12 hours significantly decreased blood glucose and serum fructosamine concentrations and was associated with good or moderate efficacy (determined on the basis of body weight stability, results of physical examination, and assessments of glycemic control) in 8 of the 10 dogs. Other than hypoglycemia, no adverse events were observed. Results suggested, therefore, that insulin detemir may be an acceptable alternative to other types of insulin that have been used to manage diabetes mellitus in dogs.2–6,17,18

Insulin glargine and insulin detemir reportedly have similar effects in humans.19 Insulin detemir likely has different pharmacokinetics in dogs than in humans, and its higher potency in dogs, compared with other insulin types, may be attributable to the concentration of insulin in current preparations, which is 4 times as high (24 mmol/L) as the concentration of insulin in NPH insulin and insulin glargine (6 mmol/L).13 Also, it is possible that the albumin-binding capacity of insulin detemir in dogs differs from that in humans, making it more potent. Thus, further studies are required to clarify the pharmacodynamics of insulin detemir in dogs. Because of the high potency of insulin detemir, our starting dosage (0.02 to 0.13 U/kg, SC, q 12 h) was markedly lower than that used in other studies2–6,17,18 aimed at evaluating other insulin types. Because of the difficulties associated with measuring small doses of insulin, we elected to use a starting dosage of 1 U/dog, SC, every 12 hours, which explains the wide range of starting dosages when expressed in U/kg. Median dosage of insulin detemir at the end of the study was 0.12 U/kg (range, 0.05 to 0.34 U/kg), which although significantly higher than the initial dosage, was still very low and consistent with dosages used in other studies.13,20 The dosage of other insulin types required for glycemic control in diabetic dogs is typically much lower.
higher and ranges from 0.5 to 1.0 U/kg, SC, every 12 hours.

Although a significant decrease in serum fructosamine concentration was observed after 6 months of treatment, only 4 of 10 dogs had a serum fructosamine concentration < 430 µmol/L at that time. Disagreements between fructosamine concentrations and clinical signs or, more frequently, between fructosamine concentrations and results of blood glucose concentration curves have previously been observed in diabetic dogs. In 4 of 10 dogs in the present study, there was disagreement between the classification of glycemic control based on median blood glucose concentration for the blood glucose concentration curve and the classification based on serum fructosamine concentration at the end of the study period. It is possible that blood glucose concentration curve results obtained on a single day were not representative of blood glucose concentrations during the previous 2 to 3 weeks or that there may have been rebound hyperglycemia owing to the Somogyi effect. The latter may occur when an insulin preparation with a duration of effect > 12 hours is administrated every 12 hours. Although none of the blood glucose concentration curves showed a typical Somogyi effect, this possibility could not be excluded.

Low blood glucose concentration is a known complication of insulin treatment and can be fatal. Hypoglycemia was the only important adverse event observed in our study population. Owners reported clinical signs characteristic of hypoglycemia in 4 of 10 dogs; similar studies of other insulin types in dogs have reported lower rates. For instance, clinical signs compatible with hypoglycemia were reported for 38.6% of dogs treated with porcine insulin zinc suspension and 17.6% of dogs treated with protamine zinc insulin, but for no dogs treated with insulin glargine. In our study, a blood glucose concentration < 90 mg/dL was observed in 6 dogs at least once, and clinical signs potentially caused by hypoglycemia were reported by owners of 4 dogs. Most of those dogs were receiving approximately 0.1 U of insulin detemir/kg (0.045 U/lb), SC, every 12 hours at the time of hypoglycemia. Drawing up small amounts of insulin can be problematic for owners and may easily lead to errors, including administration of more insulin than required. The potency of insulin detemir also makes dosage adjustments difficult. With other insulin types, dosage changes usually range from 3% to 20%. For technical reasons, the insulin dosage was usually adjusted in increments of 0.5 U/dog in the present study. In most of the dogs, the initial insulin dosage was 1 U, SC, every 12 hours, and in those dogs, the dosage was adjusted by 50%, which is a large change. We used a specific insulin diluent to dilute insulin detemir 1:10 for a small dog (3.7 kg [8.1 lb]). Interestingly, despite its low body weight, that dog was one of the few that did not develop hypoglycemia. Dilution allowed better control of the insulin dosage and likely prevented hypoglycemia. The diluent was not used in the other dogs because it was unavailable at that time. In the authors’ opinion, the specific insulin diluent should be recommended for all dogs < 10 to 15 kg (22 to 33 lb). Without the availability of the diluent, we do not recommend use of this type of insulin in dogs weighing < 10 to 15 kg. Unfortunately, this diluent is not readily available and the producer limits the supply to use in pediatric patients and research.

For dogs in the present study, the time when the blood glucose concentration nadir occurred was highly variable, although in most instances, the nadir was observed 4, 6, or 8 hours after insulin administration. In a previous study, the time to peak effect was 8 to 10 hours, demonstrating that insulin detemir is long lasting not only in humans but also in dogs. An overlap of the effects of injections given 12 hours apart may have contributed to the variability in the time to nadir in the present study, although a lack of diet standardization may also have played a role. Some dogs were fed a mixture of moist and dry foods, and it is possible that the ratio between the 2 components changed slightly during the 6-month study. Differences in times of gastric emptying or postprandial differences in glycemia associated with variable absorption of carbohydrates as well as possible differences in the glycemic indices of the diets may also have affected the time to nadir. An unpredictable time to nadir can markedly impact diabetes mellitus treatment, and monitoring blood glucose concentration curves is therefore very important for diabetic dogs treated with insulin detemir. There was no difference in median body weight before and after 6 months of insulin detemir treatment in the present study. A similar result was observed in other studies.

The main limitation of the present study was the small number of dogs. Nevertheless, our results seemed to be sufficient to suggest that insulin detemir might be a viable treatment option for dogs with diabetes mellitus, although it should be used with caution. Another limitation was the lack of standardization of exercise and diet. A diet low in simple carbohydrates and high in fiber was recommended for all dogs, but owners were permitted to change the diet to ensure that dogs ate consistently. Another limitation was that to generate the blood glucose concentration curves, 2 glucometers were used, and this factor may have added a degree of variability in the study. However, both glucometers have been validated for use in dogs and it is unlikely that this aspect substantially influenced the results of the study.

Local immediate or delayed reactions to insulin detemir have been sporadically reported in human patients, and a small number of cases of anaphylaxis in reaction to insulin have been reported. In our study, owners did not report any local or systemic reactions. However, hair was not clipped to investigate skin reactions at the injection site, and the owners were not specifically queried about a possible skin reaction or signs of pain.

The only insulin preparation currently approved for use in dogs with diabetes mellitus is a porcine insulin zinc suspension, even though veterinarians frequently prescribe other types of insulin. Therefore, the approved product should be the initial choice in first-opinion practice. However, porcine insulin zinc suspension does not always provide optimal control of diabetes mellitus in all dogs, and other types of insulin may be more advantageous in the management of this disease.

Results of the present study indicated that insulin detemir administered SC every 12 hours is a potential treatment option for diabetic dogs. Efficacy appeared to
be comparable with that reported for insulin glargine.\textsuperscript{5,6} However, hypoglycemia was substantially more frequent. Therefore, insulin detemir should be used with caution, and the initial dosage should be much lower than that for other insulin types. The high potency of insulin detemir renders exact dosing difficult, and dilution with an appropriate diluent is recommended.