Efficacy of protamine zinc insulin for treatment of diabetes mellitus in cats

Richard W. Nelson, DVM, DACVIM; Randy C. Lynn, DVM, MS;
Colette C. Wagner-Mann, DVM, PhD; Gina M. Michels, DVM, MS

Objective—To evaluate effects of protamine zinc insulin (PZI) on control of glycemia in cats with newly diagnosed diabetes mellitus or poorly controlled diabetes.

Design—Clinical trial.

Animals—67 diabetic cats.

Procedure—34 cats with newly diagnosed diabetes and 33 cats with poorly controlled diabetes were treated with PZI twice daily for 45 days. Control of glycemia was assessed on days 7, 14, 30, and 45 by evaluation of clinical response, change in body weight, serum fructosamine concentration, blood glucose concentration measured 1, 3, 5, 7, and 9 hours after administration of PZI, lowest blood glucose concentration, and mean blood glucose concentration during the 9-hour period after administration. Adjustments in dosage of PZI were made as needed to attain control of glycemia.

Results—For all cats, a significant increase in mean dosage of PZI and significant decreases in 9-hour mean blood glucose concentration, lowest mean blood glucose concentration, and mean serum fructosamine concentration were detected. For cats with poorly controlled diabetes, 9-hour mean blood glucose concentration and mean serum fructosamine concentration were significantly decreased on day 45, compared with day 0. Ninety percent of owners reported improvement or resolution of clinical signs by day 45.

Conclusions and Clinical Relevance—Results suggest that PZI was effective for control of glycemia in cats with newly diagnosed or poorly controlled diabetes and may be used as an initial treatment or as an alternative treatment in cats that do not respond to treatment with other types of insulin. (J Am Vet Med Assoc 2001;218:38–42)

Protamine zinc insulin (PZI) is a long-acting preparation of cattle- and swine-source insulin that is used to treat diabetes mellitus in cats. Unfortunately, the original manufacturer discontinued production and distribution of PZI in December 1991. Subsequently, cattle- and swine-source and recombinant human-source ultralente, lente, and neutral protamine Hagedorn (NPH) insulin have been used to treat diabetes in cats. During the past decade, it has become apparent that establishing control of glycemia in diabetic cats may be problematic with use of these insulins, in part, because of slow absorption of ultralente insulin from the subcutaneous site of injection and because of short duration of effect of lente and NPH insulin, even when administered twice a day.

Recently, compounded preparations of PZI have been provided by pharmacists at the request of veterinarians, but these preparations have been inconsistent in improving control of glycemia in diabetic cats. In 1998, an animal health pharmaceutical company resumed production of PZI, using the same methods as the original manufacturer. Protamine zinc insulin is presently under review by the United States FDA for treating diabetes mellitus in cats. To date, only absorption kinetics of PZI administered to healthy cats and a small number of diabetic cats and a retrospective study evaluating the response of 14 diabetic cats to treatment with PZI have been published. The purpose of the study reported here was to prospectively evaluate effects of PZI on control of glycemia in cats with newly diagnosed untreated diabetes mellitus or previously treated poorly controlled diabetes.

Materials and Methods

Cats—Sixty-seven privately owned cats were evaluated. Breeds included domestic shorthair and longhair (n = 61), Siamese (4), Scottish Fold (1), and Maine Coon (1). Forty-four cats were castrated males, and 23 were spayed females. Ages ranged from 2.6 to 18 years (median, 11 years), and body weights ranged from 2.3 to 9.4 kg (5.1 to 20.7 lb; median, 5 kg [11 lb]). For each cat, the diagnosis of diabetes mellitus was made on the basis of detection of appropriate clinical signs (ie, polyphagia, polydipsia, polyuria, weight loss), hyperglycemia (blood glucose concentration, > 250 mg/dl), and glycosuria. Thirty-four of 67 cats had newly diagnosed untreated diabetes, 32 were being treated with insulin, and 1 cat was receiving glipizide at the time of entry into the study. Types of insulin included recombinant human ultralente (n = 19), NPH (8), lente (1), NPH insulin derived from swine or cattle (3), and pharmacy-compounded recombinant human PZI (1). Diabetes in the previously treated cats was considered poorly controlled on the basis of persistence of clinical signs, hyperglycemia (blood glucose nadir [lowest concentration] > 250 mg/dl during a 9-hour blood glucose curve analysis), and glycosuria that persisted despite treatment.

Study design—Cats were studied for 45 days, with 5 hospital visits (days 0, 7, 14, 30, and 45). At the initial visit (day 0), history and results of physical examination, CBC, and serum biochemical analyses (including concentrations of sodium, potassium, chloride, calcium, phosphorus, urea nitrogen, creatinine, total bilirubin, cholesterol, and glucose and activities of alanine transaminase and alkaline phosphatase) were obtained. Measurements of serum thyroxine and fructosamine concentrations, tests for FeLV and feline
immunodeficiency virus (FIV), and urinalysis were performed. A single morning blood glucose concentration was determined prior to consumption of the morning meal in untreated diabetic cats. In previously treated diabetic cats, 5 blood glucose concentrations were measured; samples were obtained 1, 3, 5, 7, and 9 hours after feeding and administration of the type and dosage of insulin or glipizide that the cat had received before the study.

Written owner consent was obtained, and treatment with PZI began the evening of day 0. Initial dosage of PZI ranged from 0.2 to 0.6 U/kg (0.09 to 0.27 U/lb) of body weight, SC, q 12 h). Veterinarians chose a dosage within this range on the basis of results of history, physical examination, body weight, and blood glucose concentration. For each cat, diet was not altered during the study, compared with the diet that had been fed before the study; daily caloric intake was divided in half and fed at the time of each injection of PZI. A daily dosage diary was provided to each owner on day 0, 7, 14, and 30. Owners recorded the dates, times of administration, and dosages of PZI. On the morning of each scheduled in-hospital evaluation, owners recorded their opinion regarding change (ie, increased, decreased, no change) in their pet’s frequency of urination, water consumption, and appetite, compared with day 0.

Control of glycemia was assessed at each follow-up visit and included review of owners’ dosage diaries and subjective opinion of response to treatment, complete physical examination, measurement of body weight, and evaluation of results of blood glucose concentration determinations. The PZI was administered by owners, and cats were fed prior to evaluation at the hospital. Blood samples were obtained by use of repeated venipuncture. Adjustments in dosage of insulin were made as needed, with the intent to maintain most blood glucose concentrations between 100 and 300 mg/dl and blood glucose nadir between 80 and 150 mg/dl.

Variables assessed in this study included subjective owner opinion of response to treatment with PZI, change in body weight, serum fructosamine concentration, blood glucose concentrations determined after injection of PZI, blood glucose nadir, and mean blood glucose concentration for samples obtained 1, 3, 5, 7, and 9 hours after administration of PZI. All variables were assessed at each evaluation, except serum fructosamine concentration, which was assessed on days 14, 30, and 45. For purposes of this study, treatment with PZI was considered effective if owners reported improvement in clinical signs, mean blood glucose concentration of antimicrobials. Serum thyroxine concentration was within reference range and FeLV and FIV test results were negative in all cats. None of the cats had received glucocorticoids or megestrol acetate during the previous 1 or 6 months, respectively.

Mean dosage of PZI prescribed on day 0 was 0.4 ± 0.2 U/kg (0.18 ± 0.09 U/lb)/injection. There was a significant (P < 0.001) increase in mean dosage of PZI as the study progressed (Table 1). Mean dosage of PZI on day 45 was 0.9 ± 0.4 U/kg (0.41 ± 0.18 U/lb)/injection. Mean blood glucose concentration decreased during each in-hospital evaluation, with mean blood glucose nadir occurring approximately 5 to 7 hours after administration of PZI in the 67 diabetic cats (Fig 1). As a consequence, there was a significant (P < 0.001) decrease in 9-hour mean blood glucose concentration, mean blood glucose nadir, and mean serum fructosamine concentration as the study progressed. By day

**Analytic methods**—Blood glucose concentrations were measured by use of a hand-held portable blood glucose monitor (PBGM). The PBGM used reflectance photometry to measure production of a colored chromogen by a glucose oxidase-peroxidase reaction. Manual wiping of blood from the test strip was not necessary. Detectable glucose concentrations were determined by use of the automated wet chemistry analyzer, ranged from −51 to 37 mg/dl. Eighty-seven percent of results determined by use of the PBGM were within 15% of values determined by use of the automated wet chemistry analyzer. Serum fructosamine concentrations were determined by use of the nitroblue tetrazolium reduction method. All serum fructosamine concentrations were determined in the principal investigator’s laboratory.

**Statistical analysis**—Quantitative measurements of glycemic control (ie, 9-hour mean blood glucose concentration, blood glucose nadir, and serum fructosamine concentration), body weight, and daily insulin dosage for the 67 diabetic cats were analyzed over time by use of Friedman repeated-measures ANOVA on ranks. When significant differences were determined, post hoc comparisons were performed by use of the Dunnett multiple comparisons test. For all cats, mean blood glucose concentrations and blood glucose nadir were analyzed over time by use of Friedman repeated-measures ANOVA on ranks. When a significant difference was determined, post hoc comparisons were performed by use of the Dunnett multiple comparisons test. Comparisons between the 2 subgroups (cats with newly diagnosed versus previously treated diabetes) at a single time point were conducted by use of the t-test for independent samples or the Mann-Whitney rank sum test (when underlying assumptions for normality or equal variances were not met). Statistical analyses were performed by use of statistical software. For statistical analysis, the single blood glucose value obtained from cats with newly diagnosed diabetes on day 0 was used in lieu of the 9-hour mean blood glucose concentration and blood glucose nadir. A value of P ≤ 0.05 was considered significant. Data are expressed as mean ± SD.

**Results**—All diabetic cats—For all 67 diabetic cats, concurrent diseases identified after review of history and results of physical examination, CBC, serum biochemical analyses, and urinalysis on day 0 included periodontal disease (n = 24), urinary tract infection (4), resolving abscess caused by cat bites (2), and otitis externa (1). Cats with urinary tract infections or abscesses caused by cat bites were treated by administration of antimicrobials. Serum thyroxine concentration was within reference range and FeLV and FIV test results were negative in all cats. None of the cats had received glucocorticoids or megestrol acetate during the previous 1 or 6 months, respectively.

Mean dosage of PZI prescribed on day 0 was 0.4 ± 0.2 U/kg (0.18 ± 0.09 U/lb)/injection. There was a significant (P < 0.001) increase in mean dosage of PZI as the study progressed (Table 1). Mean dosage of PZI on day 45 was 0.9 ± 0.4 U/kg (0.41 ± 0.18 U/lb)/injection. Mean blood glucose concentration decreased during each in-hospital evaluation, with mean blood glucose nadir occurring approximately 5 to 7 hours after administration of PZI in the 67 diabetic cats (Fig 1). As a consequence, there was a significant (P < 0.001) decrease in 9-hour mean blood glucose concentration, mean blood glucose nadir, and mean serum fructosamine concentration as the study progressed. By day

**Glycemic control**—Mean blood glucose concentration decreased during each in-hospital evaluation, with mean blood glucose nadir occurring approximately 5 to 7 hours after administration of PZI in the 67 diabetic cats (Fig 1). As a consequence, there was a significant (P < 0.001) decrease in 9-hour mean blood glucose concentration, mean blood glucose nadir, and mean serum fructosamine concentration as the study progressed. By day

**Analytic methods**—Blood glucose concentrations were measured by use of a hand-held portable blood glucose monitor (PBGM). The PBGM used reflectance photometry to measure production of a colored chromogen by a glucose oxidase-peroxidase reaction. Manual wiping of blood from the test strip was not necessary. Detectable glucose concentrations ranged from 20 to 500 mg/dl. Blood glucose concentrations < 20 mg/dl and > 500 mg/dl, respectively, registered as Lo and Hi on the PBGM; Lo and Hi results were arbitrarily assigned values of 19 and 501 mg/dl, respectively.

Results of blood glucose measurements obtained by use of the PBGM were compared with serum glucose concentrations determined from the same blood sample by use of a standard automated wet chemistry analyzer. Fifty blood samples from 23 diabetic cats not enrolled in this study were evaluated; blood glucose concentrations ranged from 45 to 350 mg/dl. Coefficient of determination (r²) was 0.94, as determined by a linear regression model of results for all blood glucose samples tested by use of the PBGM, compared with results obtained by use of the automated wet chemistry analyzer.

**Glycemic control**—Mean blood glucose concentration decreased during each in-hospital evaluation, with mean blood glucose nadir occurring approximately 5 to 7 hours after administration of PZI in the 67 diabetic cats (Fig 1). As a consequence, there was a significant (P < 0.001) decrease in 9-hour mean blood glucose concentration, mean blood glucose nadir, and mean serum fructosamine concentration as the study progressed. By day

**Analytic methods**—Blood glucose concentrations were measured by use of a hand-held portable blood glucose monitor (PBGM). The PBGM used reflectance photometry to measure production of a colored chromogen by a glucose oxidase-peroxidase reaction. Manual wiping of blood from the test strip was not necessary. Detectable glucose concentrations ranged from 20 to 500 mg/dl. Blood glucose concentrations < 20 mg/dl and > 500 mg/dl, respectively, registered as Lo and Hi on the PBGM; Lo and Hi results were arbitrarily assigned values of 19 and 501 mg/dl, respectively.

Results of blood glucose measurements obtained by use of the PBGM were compared with serum glucose concentrations determined from the same blood sample by use of a standard automated wet chemistry analyzer. Fifty blood samples from 23 diabetic cats not enrolled in this study were evaluated; blood glucose concentrations ranged from 45 to 350 mg/dl. Coefficient of determination (r²) was 0.94, as determined by a linear regression model of results for all blood glucose samples tested by use of the PBGM, compared with results obtained by use of the automated wet chemistry analyzer.

**Glycemic control**—Mean blood glucose concentration decreased during each in-hospital evaluation, with mean blood glucose nadir occurring approximately 5 to 7 hours after administration of PZI in the 67 diabetic cats (Fig 1). As a consequence, there was a significant (P < 0.001) decrease in 9-hour mean blood glucose concentration, mean blood glucose nadir, and mean serum fructosamine concentration as the study progressed. By day

**Analytic methods**—Blood glucose concentrations were measured by use of a hand-held portable blood glucose monitor (PBGM). The PBGM used reflectance photometry to measure production of a colored chromogen by a glucose oxidase-peroxidase reaction. Manual wiping of blood from the test strip was not necessary. Detectable glucose concentrations ranged from 20 to 500 mg/dl. Blood glucose concentrations < 20 mg/dl and > 500 mg/dl, respectively, registered as Lo and Hi on the PBGM; Lo and Hi results were arbitrarily assigned values of 19 and 501 mg/dl, respectively.

Results of blood glucose measurements obtained by use of the PBGM were compared with serum glucose concentrations determined from the same blood sample by use of a standard automated wet chemistry analyzer. Fifty blood samples from 23 diabetic cats not enrolled in this study were evaluated; blood glucose concentrations ranged from 45 to 350 mg/dl. Coefficient of determination (r²) was 0.94, as determined by a linear regression model of results for all blood glucose samples tested by use of the PBGM, compared with results obtained by use of the automated wet chemistry analyzer.
Table 1—Variables (mean ± SD [range]) used to assess control of glycemia in 67 cats with naturally acquired diabetes mellitus treated with protamine zinc insulin twice daily for 45 days; treatment was initiated during the evening of day 0.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 30</th>
<th>Day 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin dosage (U/kg/injection)</td>
<td>NA</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2a</td>
<td>0.9 ± 0.4b</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>5.2 ± 1.4</td>
<td>5.3 ± 1.4</td>
<td>5.4 ± 1.4</td>
<td>5.6 ± 1.4</td>
<td>5.7 ± 1.4</td>
</tr>
<tr>
<td>9-hour mean blood glucose concentration (mg/dl)*</td>
<td>420 ± 611</td>
<td>380 ± 89b</td>
<td>326 ± 118a</td>
<td>261 ± 102b</td>
<td>218 ± 99b,c,d</td>
</tr>
<tr>
<td>Time of blood glucose nadir (h)</td>
<td>NA</td>
<td>4.8 ± 2.7</td>
<td>5.7 ± 2.6</td>
<td>5.4 ± 2.8</td>
<td>5.8 ± 2.7</td>
</tr>
<tr>
<td>Serum fructosamine (µmol/L)</td>
<td>598 ± 110</td>
<td>NA</td>
<td>546 ± 130c</td>
<td>481 ± 141c</td>
<td>419 ± 126c,d</td>
</tr>
</tbody>
</table>

*Values were calculated from blood glucose concentrations measured 1, 3, 5, 7, and 9 hours after administration of insulin. Values were calculated from single blood glucose concentration obtained in 34 cats with newly diagnosed diabetes and from a 9-hour serial glucose curve determined after administration of insulin (n = 32) or glipizide (1) prior to entry into the study in 33 cats with previously treated diabetes. Value significantly (P < 0.05) different from value obtained on day 0. Value significantly (P < 0.05) different from value obtained on day 7. Value significantly (P < 0.05) different from value obtained on day 14. Value significantly (P < 0.05) different from value obtained on day 30. NA = Not available.

![Figure 1](image)

Figure 1—Mean blood glucose concentrations in 67 cats with naturally acquired diabetes mellitus treated by administration of various dosages of protamine zinc insulin twice daily for 45 days. Arrows indicate time of administration of protamine zinc insulin and consumption of half of daily caloric intake, which occurred 1 hour prior to first blood glucose measurement on each day of evaluation. Mean (± SD) daily insulin dosage was 0.4 ± 0.1 U/kg (0.18 ± 0.05 µg/lb) of body weight on day 7 (solid line), 0.7 ± 0.2 U/kg (0.32 ± 0.09 µg/lb) on day 14 (dashes), 0.8 ± 0.3 U/kg (0.36 ± 0.14 µg/lb) on day 30 (dashes and dots), and 0.9 ± 0.4 U/kg (0.41 ± 0.18 µg/lb) on day 45 (dots). Value significantly (P < 0.05) different from value obtained on day 7. Value significantly (P < 0.05) different from value obtained on day 14. Value significantly (P < 0.05) different from value obtained on day 30.

45, mean 9-hour blood glucose concentration, blood glucose nadir, and serum fructosamine concentration had decreased 202 mg/dl, 226 mg/dl, and 179 µmol/L, respectively, compared with corresponding mean values on day 0. In addition, the number of Hi readings on the PBGM decreased from 20% of 203 and 335 blood glucose measurements on day 0 and 7, respectively, to 2% of 335 blood glucose measurements on day 45. Ninety percent of owners believed their pet’s frequency of urination, water consumption, and appetite had decreased during the study, and most owners believed their cat’s urination habits, water consumption, and appetite were normal by day 45. There was also a significant (P < 0.05) increase in mean body weight by day 45, compared with day 0. Body weight increased by > 0.5 kg (1.1 lb) in 50 of 67 (75%) cats by day 45.

Clinical signs of hypoglycemia developed in 5 cats and resolved with feeding (n = 3) or IV administration of glucose (2) and decreasing the dosage of PZI. Median dosage of insulin at the time signs of hypoglycemia developed was 0.5 U/kg (0.23 U/lb)/injection (range, 0.3 to 0.7 U/kg (0.14 to 0.32 U/lb)/injection). Hypoglycemia (blood glucose nadir, < 80 mg/dl) without clinical signs was identified in 24 of 268 (9%) 9-hour serial blood glucose curves and in 21 of 67 (31%) cats. Median dosage of insulin that caused the low blood glucose nadir was 0.8 U/kg (0.36 U/lb)/injection (range, 0.4 to 1.4 U/kg (0.81 to 0.64 U/lb)/injection).

Serum fructosamine concentration, 9-hour mean blood glucose concentration, and blood glucose nadir decreased to < 500 µmol/L, 300 mg/dl, and 200 mg/dl, respectively, in 57 of 67 (85%) cats and remained greater than these values in 10 cats by day 45 of treatment with PZI. Seven of the 10 cats that had high glycemic values at day 45 had previously treated poorly controlled diabetes.

Interestingly, owners of 9 of the 10 cats reported improvement in clinical signs by day 45. Four additional diabetic cats had serum fructosamine concentration > 500 µmol/L at day 45. Median insulin dosage in the 53 cats with serum fructosamine concentration < 500 µmol/L at day 45 was 0.8 U/kg (0.36 U/lb)/injection (range, 0.2 to 1.6 U/kg (0.09 to 0.73 U/lb)/injection), compared with median insulin dosage of 1.2 U/kg (0.55 U/lb)/injection (range, 0.6 to 1.8 U/kg (0.27 to 0.82 U/lb)/injection) in the 14 cats with serum fructosamine concentration > 500 µmol/L at day 45. Sixty-six of 67 (98.5%) cats had improvement in 1 or more of the measurements used to assess control of glycemia (ie, clinical signs, 9-hour mean blood glucose concentration, blood glucose nadir, serum fructosamine concentration) by day 45 of treatment with PZI.
Cats with previously treated, poorly controlled diabetes—For these 33 cats, daily insulin dosage was significantly (P < 0.001) decreased at day 45 of treatment with PZI, compared with dosage of insulin administered at day 0 (1.0 ± 0.4 U/kg [0.45 ± 0.18 U/lb]/24 h vs 1.7 ± 2.1 U/kg [0.77 ± 0.95 U/lb]/24 h, respectively). Although daily dosage of PZI was decreased, mean 9-hour blood glucose concentration (220 ± 99 mg/dl vs 372 ± 48 mg/dl), blood glucose nadir (154 ± 80 mg/dl vs 308 ± 62 mg/dl), and serum fructosamine concentration (461 ± 140 µmol/L vs 598 ± 123 µmol/L) were significantly (P < 0.001) decreased at day 45 of treatment with PZI, compared with previous insulin treatment at day 0, respectively. Twenty-three of 33 (70%) previously treated diabetic cats had serum fructosamine concentration < 500 µmol/L, 22 (67%) had 9-hour mean blood glucose concentration < 300 mg/dl, and 18 (55%) had blood glucose nadir < 200 mg/dl at day 45. Twenty-nine of 33 (88%) owners reported improvement in clinical signs by day 45 of treatment with PZI.

Cats with newly diagnosed, untreated diabetes—Mean dosage of PZI administered on day 0 and day 45 was 0.4 ± 0.2 and 0.8 ± 0.4 U/kg (0.18 ± 0.09 and 0.36 ± 0.18 U/lb)/injection, respectively. Mean 9-hour blood glucose concentration decreased from 441 ± 61 mg/dl to 185 ± 77 mg/dl (P < 0.001), blood glucose nadir decreased from 441 ± 61 mg/dl to 136 ± 67 mg/dl (P < 0.001), and serum fructosamine concentration decreased from 599 ± 99 µmol/L to 379 ± 101 µmol/L (P < 0.001) by day 45 of treatment with PZI, compared with day 0, respectively. Thirty of 34 (88%) cats with newly diagnosed diabetes had serum fructosamine concentrations < 500 µmol/L and 9-hour mean blood glucose concentrations < 300 mg/dl, and 26 (76%) cats had blood glucose nadir < 200 mg/dl at day 45. Thirty-two of 34 (94%) owners reported improvement in clinical signs by day 45 of treatment with PZI. All 34 cats with newly diagnosed diabetes improved in 1 or more of the measurements used to assess control of glycemia by day 45 of treatment with PZI.

In general, cats with newly diagnosed diabetes had a better glycemic response to treatment with PZI than cats with previously treated diabetes. Although mean daily insulin dosage was not significantly different between the 2 subgroups (newly diagnosed, 0.8 ± 0.4 U/kg/injection; previously treated, 1.0 ± 0.4 U/kg/injection; P = 0.1), mean 9-hour blood glucose concentrations (185 ± 77 mg/dl vs 220 ± 99 mg/dl; P = 0.008), blood glucose nadir (136 ± 67 mg/dl vs 154 ± 80 mg/dl; P = 0.05), and serum fructosamine concentrations (379 ± 101 µmol/L vs 461 ± 140 µmol/L; P = 0.04) were significantly decreased in cats with newly diagnosed diabetes, compared with cats with previously treated diabetes, respectively, at day 45.

Discussion
Administration of PZI was effective in decreasing blood glucose concentrations and improving clinical signs within 45 days of initiating treatment in approximately 90% of diabetic cats evaluated in this study. The only adverse effect associated with treatment with PZI was hypoglycemia, which was identified during the 9-hour serial blood glucose curve at least once during the study in 31% of diabetic cats and resulted in clinical signs of hypoglycemia in 7% of diabetic cats. All cats consumed their morning meal prior to admission to the hospital, suggesting that hypoglycemia was a result of an overdose of insulin. Considerable overlap in the range of dosages of PZI that induced hypoglycemia, established control of glycemia, and had not established control of glycemia by day 45 was identified in this study. Predicting an effective dosage of PZI that does not cause hypoglycemia in diabetic cats is difficult. Hypoglycemia developed at dosages of PZI as low as 0.15 U/kg (0.07 U/lb)/injection, suggesting that the dosage of PZI should be low when initially treating diabetic cats. Subsequent increases in the dosage of PZI should be based on owner perception of their cat’s response to treatment with PZI, changes in results of physical examination and body weight, and results of blood glucose and serum fructosamine measurements.

Historically, PZI was often administered only once per day to diabetic cats—a frequency of administration that was based more on clinical perceptions of response to treatment than on results of absorption kinetic studies. Studies have identified substantial variability in absorption kinetics of PZI among cats. Time to peak blood insulin concentration ranged from 4 to 12 hours, time of the blood glucose nadir ranged from 1 to 12 hours, and time for blood insulin concentration to return to baseline ranged from 8 to 24 hours after SC administration of PZI to healthy and diabetic cats. Protamine zinc insulin was administered twice daily in our study because of prior clinical experiences of one investigator (RWN), who found that control of glycemia was better in most diabetic cats when PZI was administered at 12-hour intervals. Although absorption kinetics were not performed, and efficacy of once-daily treatments were not evaluated in our study, mean time of blood glucose nadir was between 5 and 7 hours, and subsequent blood glucose concentrations were increasing in most cats by 9 hours after administration of PZI. These results suggest that most diabetic cats probably need PZI twice a day to maintain control of glycemia. However, blood glucose concentrations were still decreasing 9 hours after administration of PZI in 25% of cats on day 45, suggesting that once-daily administration of PZI may be effective in maintaining control of glycemia in some cats. Once-daily administration should be considered in those cats with blood glucose nadir that develops 10 hours or longer after administration of PZI, especially if hypoglycemia or the Somogyi phenomenon (insulin-induced hypoglycemia and subsequent rebound hyperglycemia) become recurring problems.30

Cats with newly diagnosed diabetes were more responsive to the glucose-lowering effect of PZI, compared with cats with previously treated diabetes. The reason for this discrepancy is not known, although differences in responsiveness to PZI between the 2 groups of cats may be attributable, in part, to selecting only previously treated cats with poorly controlled diabetes. Intuitively, the existence of concurrent unrecognized disorders, such as chronic pancreatitis, that interfere
with insulin sensitivity is more likely in cats with poorly controlled diabetes. Prior treatment with insulin may also affect the amount of insulin that is degraded at the site of injection, compared with the amount of insulin that is absorbed, and alter effectiveness of insulin secondary to formation of antibodies against insulin.11,12,13 Type of diet fed to diabetic cats also may affect control of glycemia.13 In the study reported here, several commercial and homemade diets were fed. Although feeding all cats the same diet prior to entry into the study was not attempted, each cat’s diet was kept constant throughout the study; thereby negating diet as a possible factor for improved control of glycemia in each cat. Because of the large number of diets fed in our study, the impact of any specific diet (eg, fiber-containing diets) on response of cats to treatment with PZI was not known. Regardless, PZI was effective in significantly improving control of glycemia in each cat. Because of the slow absorption of insulin from the subcutaneous site of deposition (ultralente insulin)13 and inadequate duration of effect (NPH insulin).2,4,6 Presumably, administration of PZI was effective in improving control of glycemia in some cats because of better absorption and longer duration of effect than ultralente and NPH insulin.

Blood glucose and serum fructosamine values had not decreased below arbitrary values used to identify effectiveness of PZI in 7 cats with previously treated poorly controlled diabetes and 3 cats with newly diagnosed diabetes by day 45 of treatment with PZI. Possible explanations for this apparent ineffectiveness include inadequate dosage of PZI, Somogyi phenomenon, insulin resistance induced by concurrent disorders (eg, hyperadrenocorticism, acromegaly) that were not detected by physical examination and routine blood analyses, problems with owner compliance, and lack of response to PZI for unknown reasons. Glycemic response to treatment with an alternative type of insulin (eg, lente) in diabetic cats that failed to respond to treatment with PZI was not evaluated in our study. However, treatment with an alternative type of insulin seems warranted when a cause for lack of response to PZI cannot be identified.

Administration of PZI was effective in establishing control of glycemia in cats with newly diagnosed diabetes and significantly improved control of glycemia in most cats with poorly controlled diabetes that were being treated with insulin at the time of entry into the study. Results of blood glucose measurements obtained throughout the day suggest that twice-daily administration of PZI is appropriate for most diabetic cats. The initial dosage of PZI should be low (eg, 1 U/injection) to avoid hypoglycemia, and subsequent increases in the dosage of PZI should be made on the basis of response to treatment and results of blood glucose and serum fructosamine measurements.

The authors thank the PZI Clinical Study Group, which comprised clinicians who investigated efficacy of protamine zinc insulin (PZI) for the purpose of obtaining FDA approval for treatment of cats with diabetes mellitus. In addition to the authors, members of the group were Kim Arnold, DVM; Jane Brunt, DVM; Carla L. Gartrell, DVM; Edward J. Jezbera, DVM; Gary D. Norsworthy, DVM; Julie G. Packard, DVM; James C. Prueter, DVM; DACVIM; Marilyn E. Stiff, DVM, DACVIM; Justin H. Straus, DVM, DACVIM; J. Lynn Turner, DVM, DACVIM; Elaine Wexler-Mitchell, DVM; and Jim C. Vulgamott, DVM, DACVIM.

References