Evaluation of transdermal application of glipizide in a pluronic lecithin gel to healthy cats

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Objective—To evaluate plasma glipizide concentration and its relationship to plasma glucose and serum insulin concentrations in healthy cats administered glipizide orally or transdermally.

Animals—15 healthy adult laboratory-raised cats.

Procedure—Cats were randomly assigned to 2 treatment groups (5 mg of glipizide, PO or transdermally) and a control group. Blood samples were collected 0, 10, 20, 30, 45, 60, 90, and 120 minutes and 4, 6, 10, 14, and 24 hours after administration to determine concentrations of insulin, glucose, and glipizide.

Results—Glipizide was detected in all treated cats. Mean ± SD transdermal absorption was 20 ± 14% of oral absorption. Mean maximum glipizide concentration was reached 5.0 ± 3.5 hours after oral and 16.0 ± 4.5 hours after transdermal administration. Elimination half-life was variable (16.8 ± 12 hours orally and 15.6 ± 15.3 hours transdermally). Plasma glucose concentrations decreased in all treated cats, compared with concentrations in control cats. Plasma glucose concentrations were significantly lower 2 to 6 hours after oral administration, compared with after transdermal application; concentrations were similar between treatment groups and significantly lower than for control cats 10 to 24 hours after treatment.

Conclusions and Clinical Relevance—Transdermal absorption of glipizide was low and inconsistent, but analysis of our results indicated that it did affect plasma glucose concentrations. Transdermal administration of glipizide is not equivalent to oral administration. Formulation, absorption, and stability studies are required before clinical analysis can be performed. Transdermal administration of glipizide cannot be recommended for clinical use at this time. (Am J Vet Res 2005;66:581–588)

Diabetes mellitus is one of the most common endocrine diseases in domestic cats, affecting 1 in every 400 cats in the United States. Although the prevalence of type 1 and type 2 diabetes in cats is not known, there is evidence to suggest that many cats may develop a non–insulin-dependent diabetes mellitus similar to type 2 diabetes in humans. Injectable insulin and orally administered hypoglycemic agents are treatments for humans and cats with diabetes mellitus. Approximately 10% of diabetic cats develop clinical hypoglycemia associated with insulin treatment. Orally administered hypoglycemic agents may provide a safe treatment alternative for animals in insulin crises. Glipizide, a sulfonylurea compound, is an orally administered hypoglycemic agent used in humans and cats with diabetes mellitus. It can increase insulin release from pancreatic β cells to enhance insulin sensitivity of the insulin-dependent glucose transporter receptors in peripheral tissues and reduce clearance of circulating insulin from the blood in humans with type 2 diabetes. In other studies, 38% to 65% of diabetic cats responded to short-term oral administration of glipizide with a decrease in blood glucose concentrations and improvement in clinical condition. Oral administration of glipizide has been associated with decreased blood glucose concentrations and increased serum insulin concentrations in healthy cats. Although studies have been performed to evaluate glycemic response to oral administration of glipizide in cats, the authors are not aware of any glipizide pharmacokinetic studies performed in cats nor any studies to establish the relationship between plasma glipizide concentrations and glucose concentrations in cats. Humans reportedly have an annual risk of 1.8% for adverse effects, including hypoglycemia, associated with glipizide administration. Although adverse effects have been reported in cats orally administered glipizide, the authors are not aware of any reports of hypoglycemic crises in cats. Glipizide can increase amyloidosis of pancreatic islets in cats with experimentally induced diabetes. Orally administered glipizide is, in general, tolerated well by cats; however, vomiting, anorexia, and an increase in serum liver enzyme activities have been associated with glipizide treatment in approximately 15% of treated cats. In addition, it may be difficult for many cat owners to have long-term compliance for orally administered drugs, especially with ill-tempered or inappetent diabetic cats. Oral absorption may also be impaired in cats with concurrent malabsorption disorders or gastrointestinal tract disease.

Medications have been administered to cats via the transdermal route with the aims of avoiding adverse effects of the gastrointestinal tract, providing more convenient dosing for pet owners, and improving com-
Transdermal application of drugs to cats has usually not been covered with hair. The most common site for transdermal administration has been the inside of a cat’s ear because this location cannot be licked with the tongue and is usually not covered with hair.

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Materials and Methods

Animals—Sixteen research-bred domestic shorthair cats (6 neutered males and 10 spayed females) were used in the study. Body weight ranged from 2.9 to 5.6 kg. Each cat was apparently healthy as determined on the basis of results of a physical examination, CBC count, serum biochemical analysis, urinalysis and measurement of serum fructosamine concentration. Cats had ad libitum access to water and commercial food formulated for cats until 12 hours prior to sample collection, at which time the food was removed for the remaining 36 hours of the study.

All procedures were approved by the Animal Care and Use Committee at Colorado State University.

Glipizide formulations—Five milligrams of powdered glipizide1 was packaged by licensed pharmacists into separate gel capsules for oral administration. An equivalent amount of powdered glipizide was compounded for topical administration by the same pharmacists into PLO,3 resulting in 5 mg of glipizide/0.1 mL of gel. Each dose was prepared separately to ensure that there was 5 mg of drug/0.1 mL of gel. There were no additional ingredients or additives in the PLO gel (ie, just the lecithin and pluronic gel). The capsules and gel formulations were freshly prepared for each dosing and administered to the cats within 2 hours after preparation. Although changes in glucose and insulin concentrations have been reported2 in cats administered the tablet form of glipizide, we chose to use the same source of glipizide powder for the transdermal preparation and the gel capsule to better compare absorption between the 2 formulations. We used an identical 5-mg dose for each route to provide a direct comparison between oral and transdermal administration.

Furthermore, the United States Pharmacopeia standard4 for dissolution of glipizide tablets allows for 85% dissolution in 45 minutes by use of an apparatus5 in a simulated intestinal fluid with a volume of 900 mL. We believed that these test conditions, which are standardized for oral absorption in humans, may have been unrealistic for cats because of various factors, including a smaller fluid volume in cats (ie, < 900 mL) and inability of simulated human intestinal fluid to mimic that of cats. Therefore, we believed that there was better assurance of dissolution of the orally administered dose when the powder was formulated in a capsule.

Experimental protocol—Each of the cats was manually restrained or sedated by IV administration of a combination of diazepam (0.2 mg/kg) and ketamine hydrochloride (2 to 4 mg/kg) to enable aseptic insertion of an 18-gauge, 28-cm catheter in a jugular vein or medial saphenous vein. Cats were allowed to acclimate to housing conditions and catheters for 24 hours. Catheters were flushed with 1 mL of heparinized saline solution (1 U of heparin/1 mL of 0.9% NaCl solution) every 6 hours to maintain patency (ie, 4 units of heparin were administered during the 24-hour acclimation period). When a cat dislodged the catheter within 18 hours after initial placement, an attempt was made to replace the catheter. When the catheter was dislodged within 6 hours prior to dosing or after collection of blood samples had begun, the cat was removed from the study and no more blood samples were collected.

Cats were randomly assigned to receive a capsule containing inert ingredients (3 cats), gel containing inert ingredients (3), a capsule containing 5 mg of glipizide (5), or topically applied gel containing 5 mg of glipizide (5). Capsules were orally administered, after which 1 mL of water was given to each cat via syringe. Transdermal gel (0.1 mL) wastopically rubbed onto the inner pinna by an investigator wearing a latex glove.

Blood samples were collected prior to administration (glipizide administration was defined as time 0) and 10, 20, 30, 45, 60, 90, 120, and 240 minutes and 6, 10, 14, 18, and 24 hours after administration. At each time point, 3.0 mL of blood was collected into a heparinized (0.5 units of heparin) syringe. Then, 2.5 mL of blood was immediately collected into a nonheparinized syringe; 1 mL of this blood sample was placed in a sodium fluoride–treated polypropylene tube,6 and the remaining 1.5 mL was placed in an untreated polypropylene tube. The 3.0 mL of heparinized blood was injected into the catheter, which was then flushed with 2.5 mL of nonheparinized saline solution. Because each cat received only 7 units of heparin during the 24-hour sample collection period, we did not consider it necessary to monitor coagulation variables.

Blood samples in sodium fluoride–treated tubes were centrifuged, and plasma was harvested and analyzed immediately to determine glucose concentration. Remaining blood samples were centrifuged, and plasma was harvested and frozen at −70°C until glipizide analysis could be performed. Serum was harvested from centrifuged coagulated blood samples and frozen at −70°C until insulin analysis could be performed.

Measurement of glucose, insulin, and glipizide concentrations—Plasma obtained from sodium fluoride–treated blood samples was analyzed by enzymatic oxidation by use of a semiautomated glucose analyzer. This machine can measure a wide range of glucose concentrations. Before initiation of the study reported here, duplicates of 8 samples with known glucose concentrations (range, 37 to 436 mg/dL) were assayed in parallel on the semiautomated glucose analyzer and another automatic analyzer to further validate results obtained. The second automatic analyzer was main-
Analysis of plasma glipizide concentrations—Plasma samples were obtained from the cats in the study and plasma fortified by the addition of various concentrations of pure analytical glipizide were assayed for glipizide content by use of reverse-phase HPLC with UV detection. Published references20–22 were used as a guide, and several modifications were then made to the assay procedure to increase efficiency and adapt the technique for the plasma volume collected from cats in the study reported here. The HPLC system consisted of a quaternary pump, degasser, automated sampler, and UV detector.26 Plasma extraction was accomplished by use of solid-phase extraction cartridges conditioned with 1 mL of methanol followed by 1 mL of 0.1M sodium phosphate buffer (monobasic; pH, 3.0). Because glipizide is a weak acid (pKa, 5.94), optimum results were obtained when conditions during extraction were maintained at pH 3.0 to 3.5 to ensure an acidic environment and maintain glipizide in nonionized form, which facilitated adsorption to the assay column and subsequent extraction. After addition of 500 µL of plasma sample, the cartridge was washed with 1.0 mL of a 0.1M sodium phosphate:methanol (95:5) solution, and the eluate was discarded. Final elution was achieved with the addition of 1.0 mL of methanol into a clean glass tube. The eluate was evaporated under a nitrogen stream in a hot water bath at North Carolina State University. Serum insulin concentrations were measured by use of commercial software.20

Variables determined were λ, the elimination half-life (T1/2), maximum plasma concentration (Cmax), and time of Cmax (Tmax). The T1/2 was defined as 0.693/λ. Values for Cmax and Tmax were determined from the plot of the time-versus-concentration curves of the samples collected. The relative fraction of the dose absorbed after transdermal application was determined by the ratio of the respective AUCs (ie, AUCtransdermal/AUCoral). Mean residence time (MRT) was calculated by use of statistical moment theory with the following equation:

\[ MRT = \frac{\text{AUMC}_{\text{area}}}{\text{AUC}_{\text{area}}} \]

where AUMCarea is the area under the moment curve from time 0 to infinity and AUCarea is the AUC from time 0 to infinity. Variables such as apparent volume of distribution and clearance were not directly calculated because a dose was not administered IV. Pharmacokinetic variables were reported as mean ± SD.

Pharmacodynamic analysis—Pharmacodynamic modeling was performed with the aid of a computer program24 and in accordance with the principles outlined by Gabrielson and Weiner.25 A simple pharmacodynamic model was used in which glipizide concentrations were plotted on the x-axis and glucose concentrations were plotted on the y-axis. A simple maximum inhibitory effect model was developed by use of assumptions that a maximum effect of glucose (Emax) and a zero (baseline) effect (E0) were observed. The equation used for the analysis was as follows:

\[ \text{Effect} = \frac{(E_{\text{max}} - E_{0})}{C} \times \left( \frac{1}{C + E_{\text{max}}} \right) \]

where C is the plasma glipizide concentration, and Emax is the drug concentration that causes a decrease in glucose concentrations in 50% of the sample population.

Statistical analysis—All statistical analyses were performed by use of commercial software.26 Plasma glucose, serum insulin, and plasma glipizide concentrations were reported as mean ± SD. Values were compared between treatment groups by use of a repeated-measures ANOVA.
Glipizide and glucose concentrations at each time point were compared between treatment groups by use of a Bonferroni-adjusted unpaired t test. Although data appeared to be normally distributed, nonparametric analyses were used for pharmacokinetic data because of the limitations of evaluating small sample sizes for normality. Pharmacokinetic variables were compared between treatment groups by use of the Mann-Whitney test. For all analyses, values of $P < 0.05$ were considered significant.

**Results**

One cat from the oral treatment group was removed from the study because it dislodged the catheter during the sample collection period. Thus, data for this cat were excluded from analyses.

Linear regression revealed an excellent correlation in glucose values between the semiautomated glucose analyzer used in this study and the automatic analyzer maintained by the Colorado State University Clinical pathology laboratory. Values for linear regression were as follows: $R^2$, 0.998; slope, 0.998; y-intercept, 3.8 mg/dL; and 98% confidence interval, −5.1 to 12.8 mg/dL.

Glucose concentrations remained stable, and glipizide was not detected in any of the control cats for the duration of the study. All cats administered glipizide, both orally and transdermally, had detectable serum glipizide concentrations at some time point during the study. Pharmacokinetic variables for oral and transdermal administration were summarized (Table 1). Cats orally administered glipizide had significantly higher peak concentrations that were reached more quickly, compared with that for cats administered glipizide transdermally (Figure 1). During the 24-hour study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>Mean</th>
<th>SD</th>
<th>$P^*$</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>$\lambda$(h)</td>
<td>Oral</td>
<td>0.05</td>
<td>0.03</td>
<td>0.72</td>
<td>0.06</td>
<td>0.002–0.060</td>
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<td>0.00</td>
<td>0.002–0.540</td>
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<td>12.0</td>
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<td>10.6</td>
<td>9.1–30.7</td>
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<td>15.3</td>
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<td>1.2–37.2</td>
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<td>$C_{max}$ ($\mu$g/mL)</td>
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<td>0.01</td>
<td>5.7</td>
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<td>0.2–1.7</td>
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<td>2,808.7</td>
<td>0.09</td>
<td>3,200.1</td>
<td>551.5–7,219.1</td>
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<td>$AUC_{\infty}$ ([min × $\mu$g/mL])</td>
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<td>2,386</td>
<td>0.03</td>
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<td>$MRT$ (h)</td>
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<td>18</td>
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<td>14.33</td>
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<td>ND</td>
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</table>

$^*$Values differed significantly ($P < 0.05$) between the 2 treatment groups (nonparametric Mann-Whitney test).

$\lambda$ = Elimination rate constant. $T_{1/2}$ = Elimination rate half-life. $T_{max}$ = Time to reach maximum plasma concentration. $C_{max}$ = Maximum plasma concentration. $AUC_{0-Cn}$ = Area under the plasma concentration-versus-time curve from 0 to the last time point. $AUC_{\infty}$ = Area under the plasma concentration-versus-time curve from 0 to infinity. $MRT$ = Mean residence time. $F$ = Bioavailability (ie, fraction of transdermally administered drug absorbed, compared with the amount of drug absorbed after oral administration). NA = Not applicable. ND = Not determined.

![Figure 1](image1.png)

Figure 1—Plasma glipizide concentrations for each of 4 healthy cats administered a single dose (5 mg) of glipizide PO (solid symbols) and for each of 5 healthy cats administered a single dose (5 mg) of glipizide transdermally (open symbols). Each symbol represents a concentration for 1 cat. Time of administration of glipizide was defined as time 0. Notice that all data points on the x-axis are at equal increments, but the intervals are not all equivalent.
period, a single transdermally administered dose of 5 mg of glipizide resulted in 20% relative absorption, compared with that for a single orally administered 5-mg dose. Although the $\text{T}_{1/2}$ was similar regardless of the route of administration, the high variability of absorption detected for both treatment groups precluded reliable interpretation of the data.

All cats treated with glipizide, both orally and transdermally, had a significant decrease in mean plasma glucose concentrations, compared with glucose concentrations for control cats (Figure 2). Cats orally administered the drug had a faster decrease in glucose concentration that was of greater magnitude, compared with that for cats administered the transdermal preparation. Although there was a significant difference between mean plasma glucose concentrations of the treatment groups for hours 2 through 6 after drug administration, mean plasma glucose concentrations were similar between the treatment groups for the remainder of the study period.

Analysis of results for the pharmacodynamic model created by use of the inhibitory EMAX effect indicated that E$_{\text{MAX}}$ and E$_{\text{0}}$ were 80.72 ± 1.36 mg/dL and 38.20 ± 5.01 mg/dL, respectively. The EC$_{50}$ was 0.71 ± 0.29 µg/mL. After transdermal administration, mean plasma glipizide was higher than this value only in samples obtained 10 and 14 hours after application. After oral administration, plasma glipizide concentrations were higher than this value from hour 1 to the end of the study (i.e., 24 hours).

None of the cats had a significant change in serum insulin concentration after glipizide administration (Figure 3). There were no differences in mean insulin

![Figure 2](image-url)

**Figure 2**—Mean ± SD plasma glucose concentrations in control cats (diamonds) and healthy cats administered a single 5-mg dose of glipizide orally (squares) or transdermally (triangles). Time of administration of glipizide was defined as time 0. Notice that all data points on the x-axis are at equal increments, but the intervals are not all equivalent. The shaded area indicates the time period during which concentrations for the oral treatment group and transdermal treatment group differed significantly ($P < 0.05$) from the value for the transdermal treatment group. Within a time point, value for the control group differs significantly ($P < 0.05$) from the value for the oral treatment group.

![Figure 3](image-url)

**Figure 3**—Mean ± SD serum insulin concentrations in control cats (solid circles) and healthy cats administered a single 5-mg dose of glipizide orally (open triangles) or transdermally (solid triangles). Time of administration of glipizide was defined as time 0. Notice that all data points on the x-axis are at equal increments, but the intervals are not all equivalent. There was an insufficient amount of serum in all samples to enable us to evaluate insulin concentrations for all cats at all time points. Therefore, some of the mean concentrations represent values for 3 or 4 cats rather than the entire group.
concentrations between treatment groups. Similarly, there were no differences in insulin concentrations between the treatment groups and the control group during the course of the study.

Discussion

In the study reported here, we used a pharmacokinetic-pharmacodynamic evaluation to examine an alternative method for delivery of glipizide to cats. All cats administered glipizide, both orally and transdermally, had detectable serum glipizide concentrations and significant decreases in plasma glucose concentrations, compared with values for control cats. Because all cats treated with glipizide had a significant decrease in plasma glucose concentrations, compared with concentrations in control cats, we believe that both protocols resulted in absorption of a sufficient amount of glipizide to exert an effect. Blood glucose concentrations in cats administered glipizide orally were significantly lower 2, 4, and 6 hours after drug administration, compared with concentrations in control cats receiving the transdermal preparation and control cats. However, plasma glucose concentrations in cats receiving the transdermal preparation of glipizide then decreased so that there was no difference between treatment groups for hours 10 through 24 following drug administration. Despite differing serum glipizide concentrations, both treatment groups had a similar decrease in plasma glucose concentrations, compared with concentrations for control cats, during the latter half of the study. This may indicate that higher glipizide concentrations achieved after oral administration may not be necessary to adequately cause a decrease in glucose concentrations.

In another study,11 healthy cats given 2.5, 5, or 10 mg of glipizide PO all had a similar decrease in serum glucose concentrations within 2 hours after drug administration. Analysis of these data suggests that glipizide's effect on glucose may reach a plateau in healthy cats, after which higher concentrations would not lead to an increased response. Given that the lowest dose used in that study (2.5 mg) led to an equivalent or potentially maximal effect, it is currently unclear as to the minimum dose of glipizide that would be required to cause a decrease in glucose concentrations. It is also unclear whether glipizide's effects are solely related to plasma glucose concentrations or whether they may also be a result of currently undefined factors or effects.

The dose selected for oral administration in our study was based on recommendations in the literature and results of other studies.2-5 However, none of those studies involved measurement of the pharmacokinetics of glipizide and its relationship to glucose concentrations in cats. Although transdermal absorption is often delayed and decreased, compared with absorption after oral administration, the same 3-mg dose was chosen for oral and transdermal delivery so that we would not risk hypoglycemia in these healthy cats. Although 5 mg of glipizide is often used clinically in cats with diabetes, doses are less than 2.5 mg can reportedly cause a similar decrease in the blood glucose concentrations of healthy cats. Thus, we believed that 5 mg of glipizide administered transdermally would be adequate to decrease plasma glucose concentrations.

The pharmacodynamic modeling performed in the study revealed that the EC50 value, although variable (coefficient of variation, 41%), was 0.71 µg/mL. After oral dosing, plasma glipizide concentrations were higher than this EC50 value from hour 1 until the end of the study and were at least 3 times higher than this EC50 value for most of the study. Plasma glipizide concentrations after transdermal administration only exceeded this projected EC50 at 10 and 14 hours after application. With such low glipizide concentrations, minimal change in plasma glucose concentrations would be expected. Given that all cats that received the transdermal preparation of glipizide had a decrease in plasma glucose concentrations, the calculated EC50 may have overestimated the concentration necessary to affect glucose concentrations in these cats.

We also mention that glipizide's mechanism of action is not solely dependent on plasma concentrations of glipizide. Glucose concentrations may have also decreased for reasons other than glipizide administration. Further pharmacodynamic studies are needed to ensure the repeatability of these results and to better establish the minimum glipizide concentrations required to affect glycemic variables in healthy cats.

Glipizide was detected earlier and in higher concentrations in the plasma of cats administered the drug orally. The relative systemic absorption of a transdermal preparation of 5 mg of glipizide, compared with that for the orally administered dose, was only 20% with high variability. Analysis of these findings suggests an incomplete, inconsistent, and delayed absorption for transdermal delivery, compared with that for oral administration. Many barriers in the skin are responsible for limiting transdermal absorption of drugs.11,28,30 Skin thickness, absorption surface area, permeability, blood flow, and skin temperature affect transdermal delivery.27,28 In addition, a drug must be soluble in the carrier compound and sufficiently lipophilic to penetrate the skin.27,30 As a weak acid (pKa, 5.94), the formulation and skin surface would have to be acidic to optimize the lipophilicity of the drug. The drug dosage may need to be increased when applied to a small region of skin such as the inner pinna, and drug potency must be sufficiently high to allow for small, effective dose administration.

Although not tested in our study, we cannot be assured that repeated application of the transdermal preparation of glipizide in the PLO vehicle would be safe for the skin. No visible skin irritation was evident in the cats of our study after 1 application, and many veterinary transdermal studies4,5,23 have used pluronic organogels as transdermal carriers without adverse effects. Dermal irritation was reported48 after repeated applications of a transdermal formulation of fluoxetine in a PLO gel in cats on which the gel was applied to the inner pinna. Despite this irritation, absorption of only 10% (relative to orally administered fluoxetine) was reported in that study.

In the study reported here, both treatment groups had variable, inconsistent glipizide absorption. Because sample size was small, additional studies that
use a larger sample population and multiple doses of transdermally applied glipizide are needed to determine whether it is possible to achieve higher plasma concentrations or a steady-state concentration over time. Despite the inconsistent plasma glipizide concentrations and consistent decrease in plasma glucose concentrations, neither treatment group had a significant change in serum insulin concentrations, compared with concentrations for control cats. This is in contrast to the data in another study in which investigators documented an increase in serum insulin concentrations within minutes after oral administration of glipizide to healthy cats, with peak insulin concentrations achieved after approximately 15 minutes. Healthy humans orally administered glipizide have also had rapid increases in insulin concentrations directly after drug administration.11

We do not have an apparent explanation for the lack of insulin response in the study reported here. Glipizide powder was encapsulated into gel capsules and administered orally, whereas in investigations in another study10 administered glipizide in tablet form. It is impossible to determine whether the drug formulation induced a difference in effect because plasma glipizide concentrations were not measured in that other study.12 In a pharmacodynamic study in humans, investigators reported increased insulin concentrations only when glipizide concentrations were > 200 ng/mL, despite a prolonged, persistent hypoglycemia in the face of undetectable drug concentrations and insulin concentrations similar to those of the control group. Improper sample collection, storage, shipping, or equipment calibration could also have affected the measurement of insulin concentrations. Serum insulin concentrations were measured by use of an assay validated for use in samples obtained from cats.10 Despite the lack of a detectable serum insulin response, sustained hypoglycemia was achieved in both treatment groups. This is similar to some studies13–14 in humans in which there was prolonged control of glucose concentrations after adjustment of insulin concentrations and clearance of detectable glipizide. Analysis of these data suggests that glucose may have decreased in response to extrapancreatic effects on sensitivity of target tissues to insulin with the formulations of glipizide used in our study.

Finally, it is important to mention that glipizide reportedly causes adverse effects in the gastrointestinal tract and subclinical hypoglycemia in cats. Although persistent hypoglycemia was seen during oxidative analysis for both treatment groups in the study reported here, no clinical evidence of hypoglycemia (ie, vomiting, diarrhea, weakness, ataxia, trembling, or stupor) was detected. Transdermal application of glipizide resulted in detectable plasma concentrations in all cats. It appeared to be marginally and variably absorbed, compared with absorption after oral administration. There was some evidence that transdermal application of glipizide resulted in a decrease in plasma glucose concentrations in healthy cats. However, we cannot extrapolate these findings to clinical use in diabetic cats without more data. On the basis of our limited study reported here, transdermal application of glipizide cannot be recommended for clinical use without further study. Transdermal administration (dose concentration, dosing interval, and drug carrier), preparation stability, and safety after application remain unknown. Long-term studies are needed in cats with naturally developing diabetes mellitus to determine whether this will be a feasible therapeutic option.

References