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Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control

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Abstract

The aim of this study was to report outcomes using detemir and a protocol aimed at intensive blood glucose control with home monitoring in diabetic cats, and to compare the results with a previous study using the same protocol with glargine. Eighteen cats diagnosed with diabetes and previously treated with other insulins were included in the study. Data was provided by owners who joined the online German Diabetes-Katzen Forum. The overall remission rate was 67%. For cats that began the protocol before or after 6 months of diagnosis, remission rates were 81% and 42%, respectively ($P = 0.14$). No significant differences were identified between the outcomes for the glargine and detemir studies, with the exception of three possibly interrelated factors: a slightly older median age of the detemir cohort at diabetes diagnosis, a higher rate of chronic renal disease in the detemir cohort and lower maximal dose for insulin detemir.

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Introduction

There are no reported studies of the use of insulin detemir in diabetic cats. Detemir (Levemir; Novo Nordisk) is a long-acting human insulin analogue that was approved by the Food and Drug Administration for human use for the US market in 2005.[1] In this insulin analogue, the B30 amino acid threonine has been removed. Additionally, a 14-carbon, myristoyl fatty acid is covalently bound to lysine at position B29. Insulin detemir reversibly binds to albumin via its fatty-chain, which increases the duration of action of the insulin.[2]

Detemir's mechanism of action differs substantially from that of insulin glargine (Lantus; Sanofi Aventis), the only other long-acting insulin analogue that currently has FDA approval for use in humans. In glargine, the asparagine at position A21 has been replaced by glycine, and two arginines have been added to the B chain at positions 31 and 32. The effect of these changes is that glargine is soluble in an acidic solution, but, on injection, forms a deposit in the neutral pH of subcutaneous tissue from which it is slowly released.[2]

The efficacy of twice-daily administration of glargine has been examined in four studies in diabetic cats. The only controlled, prospective study in newly-diagnosed diabetic cats compared glycaemic control and remission rates between three insulins.[3] Cats were fed a very low carbohydrate diet (<8–10% metabolisable energy (ME)) and blood glucose curves were initially performed weekly, with insulin dose adjustment based on an algorithm. The reported remission rate for glargine was 8/8 cats, which was significantly higher than for protamine zinc insulin (PZI) (3/8) and porcine lente insulin (2/8). Glargine also provided better glycaemic control. The largest study reported involved 55 diabetic cats, 91% of which were previously treated with another insulin, predominantly porcine lente, for a median of 15 weeks.[4] Cats were treated with glargine, fed a very low carbohydrate (<6% ME) diet and monitored using home blood glucose measurements at least three times daily. Insulin dose was adjusted using an algorithm aimed at achieving euglycaemia. High remission rates (84%) were achieved provided the protocol was initiated within 6 months of

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diagnosis, with an overall remission rate of 64% for all cats irrespective of when the protocol was initiated after diagnosis. Two other small studies (8/12 cats, respectively) reported lower remission rates (12–40%). In both studies, cats were predominantly previously-treated diabetic cats, but no information was provided on duration of previous treatment. In one study, 2/5 cats completing the 12-week study were in remission[5] and in the other study 2/12 were in remission after 10 weeks, although only six cats were fed a very low carbohydrate diet.[6] Because of the negative impact of the duration of diabetes on the probability of remission, evaluation of remission rates associated with glargine treatment is difficult in these two studies. In a fifth study, once-daily dosing of glargine did not result in better glycaemic control than twice-daily administration of porcine lente insulin.[7]

The pharmacodynamics of glargine has been evaluated in two studies in healthy cats. In a three-way crossover study of glargine, PZI and lente insulins in nine healthy cats, it was found that the mean time to first nadir glucose was 14 h for glargine [substantially longer than for either PZI (4 h) or lente (5 h)]. Cats injected with glargine also had a longer duration of action when compared with lente, but not PZI.[8] In a two-way crossover study of once-daily versus twice-daily administration of glargine in six healthy cats (once-daily dose of 0.5 IU/kg or twice-daily dose of 0.25 IU/kg, repeated after 12 h), it was found that the time to reach last glucose nadir differed, with longer intervals occurring following twice-daily dosing.[9]

Finally, only one study currently exists in which glargine and detemir have been directly compared in cats. However, this comparison was performed in healthy cats using an isoglycaemic clamp method. Detemir was found to have a statistically significant slightly later onset of action in healthy cats (1.8 ± 0.8 h for detemir and 1.3 ± 0.5 h for glargine, $P = 0.03$). The end of action and time-to-peak action were not found to be significantly different. It was also found that both insulins have shorter durations of action in cats than in humans and are thus considered to be most effective as twice-a-day drugs in most cats.[10]

The aims of the current study were (i) to report outcomes using detemir and a protocol aimed at intensive blood glucose control with home monitoring in diabetic cats and (ii) to compare the results with a previous study using the same protocol with glargine.

Material and methods

The diabetic cats included in the study were recruited from an online forum. The German-language Diabetes-Katzen Forum (http://www.diabetes-katzen.net/forum/index.php) is a forum specifically for owners of diabetic cats. It was founded in 2004 and has existed in its current form since 2006 with more than 600 registered members. The data was provided by owners in the Forum and was reported up to December 2008.

In this cohort, 17/18 cats were initially treated with another insulin for a median of 9 weeks (range = 7 days to 1.5 years), but failed to achieve remission prior to switching to detemir. Of these previously treated cats, 16/17 cats were initially treated with porcine lente insulin (Caninsulin/Vetsulin; Intervet/Schering-Plough Animal Health). In Germany, porcine lente insulin is currently the only insulin licensed for feline use; legislation requires that it is the first insulin used in the treatment of diabetic cats. Most (88%; 15/17) treated cats were fed a low carbohydrate diet while on the other insulin, yet did not achieve remission.

The owners subsequently followed the forum protocol for intensive blood glucose regulation which was originally developed for glargine,[4] but which can also be used in the same manner with detemir. Owners were asked to carefully read the protocol when joining the forum and advised of a number of prerequisites for using the protocol. These prerequisites included using the appropriate type of glucometer; performing daily blood glucose measurements; feeding a very low carbohydrate, wet food diet; regularly testing for ketones prior to achieving regulation; and recognising and initially treating hypoglycaemia. Owners were encouraged to maintain close contact with their veterinarian with regard to their cat's diabetic treatment and general health. Advice provided in the forum related only to non-ketotic diabetic cats with signs of uncomplicated diabetes. Owners of cats that developed ketonuria, hypoglycaemia or signs indicating illness were directed to immediately seek veterinary attention.

Detemir was administered twice daily and the insulin dose was adjusted with the aim of achieving euglycaemia. Owners aimed for glucose of 50–100 mg/dl (2.8–5.5 mmol/l) as measured using a portable whole blood glucose meter calibrated for human blood. Most owners used the glucometers Accu-Chek Aviva (Roche) or Ascensia Contour (Bayer). Owners performed an average of 5 ± 2 blood glucose measurements per day in the stabilisation period.

Detemir was used for >10 weeks and/or until remission was achieved. Owners recorded and made available all blood glucose measurements and all daily insulin dosages for their cat in the form of spreadsheets. Owners also supplied as much additional clinical information as possible, which was collected in the form of questionnaires. All cats were fed only very low carbohydrate canned food (generally <8–10% of energy), or in several cats, very low carbohydrate, veterinarian-developed homemade diets.

Of 61 cats treated with detemir in the forum at the cutoff point, 43 were excluded. The exclusion criteria were: acromegaly (n = 4), less than 10 weeks of data

available and the cat was not in remission (n = 3), declined to make data available (n = 21), very little blood glucose home monitoring (required minimum of three measurements/day in stabilisation phase) or not following protocol (n = 15). The remaining 18 cats met the inclusion criteria and were included in the study.

Results

Non-insulin dependence (diabetic remission)

The overall remission rate in the cohort was 67% (12/18). For cats that began the protocol within 6 months of diagnosis, the remission rate was 81% (9/11) and the median time from diagnosis to starting protocol was 2 months (range = 7 days to 5 months). For cats that began the protocol 6 months after diagnosis, the remission rate was 42% (3/7) and the median time from diagnosis to starting protocol was 11 months (range = 6.6 months to 1.5 years).

There was no statistically significant difference in remission rate when comparing cats that started the protocol before or after 6 months in this cohort [P = 0.14, Fisher's exact test, 95% confidence interval (CI) 0.48, 89.85], which contrasts with the glargine study where the difference was highly significant (P <0.001, Fisher's exact test, 95% CI 2.42, 45.48).

The median time to remission in cats achieving non-insulin dependence was 1.7 months after beginning the intensive protocol (range = 10 days to 5.3 months). Stable remissions were achieved in 75% (9/12) cats; they remained off insulin and the median duration of remission was 12.3 months (range = 6.4 months to 2 years). Three cats (25% of remission cats) relapsed and only one relapsed cat achieved a second remission.

Insulin-dependent diabetic cats

In the cohort, 33% (6/18) cats required insulin throughout the study to control blood glucose concentrations and did not achieve remission. The median length of time on the protocol was 10 months (range = 5.4 months to 1.2 years).

Of long-term diabetics, 83% (5/6) were considered well regulated (median blood glucose concentration ≤150 mg/dl; 8.3 mmol/l) and 17% (1/6) were moderately well regulated (median blood glucose concentration ≤200 mg/dl; 11 mmol/l. There were no poorly regulated cats in this cohort.

Hypoglycaemia

Clinical hypoglycaemia was rare in the cohort and only a single event occurred in which one cat displayed mild signs consisting of restlessness and trembling. In contrast to this, biochemical hypoglycaemia was common: 6.3% of blood glucose curves had nadirs of ≥40–<50 mg/dl (≥2.2–<2.8 mmol/l), 3.2% of curves had nadirs of ≥30–<40 mg/dl (≥1.7–<2.2 mmol/l)), 0.7% of curves had nadirs of ≥20–<30 mg/dl (≥1.1–<1.7 mmol/l) and 0.04% of curves had nadirs of <20 mg/dl (<1.1 mmol/l).

Chronic renal disease in cohort

Creatinine values were available for 16 cats and 63% (10/16) of cats tested had evidence of chronic renal disease (CKD) based on persistent azotaemia (≥2 elevated creatinine values). The median age at diagnosis of CKD was 12 years (range = 9.6–14.9 years). Of the cats diagnosed with CKD, 4/10 were diagnosed before or after diabetes diagnosis, but prior to starting detemir; 3/10 were diagnosed after diabetes diagnosis, after starting detemir, but no previous test was available; 1/10 were diagnosed after diabetes diagnosis, after starting detemir with previously normal test(s); 2/10 were first diagnosed after diabetic remission and had previously normal test(s).

We compared these results with those in the glargine cohort.[4] In this previous study, 26% (13/49) of glargine-treated cats had persistent azotemia consistent with CKD. Of these, 31% were in the 10–<15 year age group and a surprisingly high number of cats had azotaemia in the 5–<10 year age group (18%). The difference in the number of cats with CKD in the detemir (10/16) and glargine (13/49) cohorts was significant (P = 0.015, Fisher's exact test, 95% CI 1.20, 18.41).

Comparison of the detemir and glargine studies

The glargine study consisted of 55 cats that were also recruited from the German Diabetes-Katzen Forum, utilising the same protocol and very similar inclusion criteria.[4] No significant differences were identified between outcomes for glargine and detemir, for example percent remission, effect of a delay in switching to the protocol on probability of remission, time to remission, relapses, etc.

However, there were three areas in which we did identify differences between the two cohorts. Firstly, the detemir cohort was slightly older than the glargine cohort at the time of diabetes diagnosis (P = 0.046): the median age at diagnosis of the detemir cohort was 11.3 years (range = 5.9–14.4 years) and the median age at diagnosis of the glargine cohort was 10.3 years (range = 3.1–16.7 years). Secondly, the rate of CKD in the detemir cohort was higher than that of the glargine cohort (P = 0.015). Thirdly, a lower maximal dose for detemir was required (P = 0.045): the median maximum glargine dose was 2.5 IU (range = 1.0–9.0 IU) and the median maximum detemir dose was 1.75 IU (range = 0.5–4.0 IU).

Discussion

The aim of this study was to report, for the first time, the outcomes of using detemir and a protocol aimed at intensive blood glucose control with home monitoring

in diabetic cats, and to compare the results with a previous study using the same protocol with glargine.

Using detemir in previously treated, diabetic cats with the intensive blood glucose control protocol appears to be equally effective as using glargine, with important factors such remission rate, time to remission, relapse and rates of hypoglycaemia (both biochemical and clinical) being very similar. Although it should be noted that the detemir cohort (18 cats) was smaller than the glargine cohort (55 cats) and some more subtle differences may only become apparent when sufficiently large numbers of cats are examined.

In contrast to glargine, there was no statistically significant difference in remission rates for detemir whether the protocol was instituted before or after 6 months of diagnosis of diabetes. However, the lack of statistical significance in the detemir cohort is likely owing to a lack of statistical power. There were very similar remission rates in both cohorts for institution of therapy prior to (81% and 84%) and after 6 months (42% and 35%) of diagnosis. However, the glargine cohort (55 cats) was much larger than the detemir cohort (18 cats). The influence of early initiation of tight glycaemic control on remission rates has important implications for the management of diabetic cats, especially considering the legal requirements for veterinarians to first use a veterinary-licensed insulin, and should be investigated further with a larger cohort.

A substantial number of detemir-treated cats were excluded from the study (43/61 being treated with detemir). The two largest groups of excluded cats consisted of those that had owners who declined to make data available (n = 21) and those that had owners who performed very little home blood glucose monitoring (fewer than three measurements per day) or were not following the protocol (n = 15). Subsequent to filling out an introductory questionnaire associated with joining the forum, the owner could then elect to become an active participant in the forum. Becoming an active participant involved starting a detailed spreadsheet containing all daily blood glucose measurements and insulin dosages. In addition, to be included in our study, the owner had to fill out a second, more detailed, questionnaire. Not many owners were willing to participate this intensively in the forum and the study, thus leading to the exclusion of 21 cats.

Of the 15 cats that were excluded owing to insufficient blood glucose testing or not following the protocol, the majority of owners were not following the protocol. Not following the protocol typically meant that owners tested frequently enough each day and fed a low carbohydrate, but did not adjust the insulin dose according to the protocol (typically nadirs were not less than 100 mg/dl in these cats). Of the 15 cats where owners did not follow the protocol, only four achieved remission (a 26% remission rate compared with the 67% remission rate seen in the study cohort).

Given that the aim of our study was to report results of a protocol aimed at euglycaemia and exclusions were based on the owner not following the protocol, we feel that the bias introduced by the exclusions is relatively minimal. In addition, while the number of cats in this detemir study (18) was relatively small, the results were consistent with those of the much larger glargine study (55 cats), thus lending support to the observed results. However, remission rates for protocols requiring less owner commitment need to be investigated and are likely to be lower.

Compared with the prevalence of CKD reported for aged cats, the prevalence of CKD appears high in our cohort of detemir-treated diabetic cats aged 10–15 years (63%), and in our previous study of glargine-treated cats aged 10–<15 years (31%) and 5–<10 years (18%). The prevalence of CKD in geriatric cats has been evaluated in a number of studies:[11] 7.7% of cats over 10 years of age were reported to have CKD,[12] 15.3 % of cats over 15 years of age[13] or 30% of cats over 15 years of age.[14] Based on creatinine values, a study of 235 cats presented at a clinic in 2005 found an incidence of 16.4% in the 12–13 year age group, 32.5% in the 14–15 year age group, 52.1% in the 16–17 year age group, 63.6% in the 18–19 year age group and 83.3% in the ≥20 year age group.[15]

In a study of six diabetic cats, histological evidence of diabetic nephropathy was documented.[16] A later study, which examined the incidence of CKD among 55 diabetic cats, showed that renal disease was common and a frequent cause of death (n = 8), but its prevalence was not different from the general cat population.[17] More recent work evaluated 66 diabetic cats, 35 non-diabetic cats with other illnesses and 11 healthy cats with a commercial assay (ERD Health Screen Feline Urine Test; Heska Corporation) to test for the prevalence of microalbuminuria and proteinuria. Microalbuminuria prevalence was significantly higher in the diabetics, as was a protein/creatinine ratio (UPC) of greater than 0.4.[18] While persistent albuminuria is considered to be a well-established marker of diabetic nephropathy in humans with type 2 diabetes, its use is not uncontroversial: a significant proportion of human diabetic patients with renal impairment exhibit normoalbuminuria and several studies have shown that only very small proportions of patients diagnosed with microalbuminuria progress to end-stage renal disease. This has led to some doubt as to the legitimacy of the use of this marker in the early detection of diabetic nephropathy in human type 2 diabetics. There are also a number of unresolved issues relating to the use of the albumin/creatinine excretion ratio in early morning urine in humans, mostly associated with a lack of standardisation and intermethod variability.[19] Therefore, the predictive

value of an increased prevalence of microalbuminuria or elevated UPC in feline diabetics should be examined in more detail.

The statistically significant differences in the age of diabetes diagnosis (higher in the detemir cohort), rate of chronic renal disease (higher in detemir cohort) and maximal insulin dose (lower in detemir cohort) in our study may well be correlated. Older cats tend to have higher rates of renal disease and in diabetic humans with CKD it has been shown that as creatinine clearance declines, the clearance of insulin diminishes and the half-life is prolonged, resulting in decreased insulin requirement.[20] In humans, the pharmacokinetics of short- and long-acting insulin preparations in patients with varying degrees of renal dysfunction have not yet been well studied. However, several broad insulin-dosing guidelines have been suggested: when the glomerular filtration rate (GFR) decreases to between 10 and 50 ml/min, the insulin dosage should be decreased by 25%, and when the GFR is less than 10 ml/min, it should be decreased by 50%.[21]

Moderate-to-severe renal insufficiency has previously been described as a cause of insulin resistance in cats.[22–24] The more recent publications also note that reduced insulin clearance may lead to an increased risk of hypoglycaemia.[22,23] However, there are no studies in diabetic or non-diabetic cats with renal disease which have examined the prevalence of either insulin resistance or an increased risk of hypoglycaemia. In humans, insulin resistance has been shown to be common in end-stage renal disease and possibly also at moderate-to-severe levels of renal insufficiency.[25] However, the studies that have demonstrated insulin resistance in patients with renal disease were performed in non-diabetic individuals,[26,27] which make an extrapolation to patients with diabetes, and the effect on their extraneous supplementary insulin requirement, difficult. Therefore, while there is extensive clinical experience in humans showing that advanced renal disease can lead to reductions in required insulin dosages, the clinical effect of insulin resistance in human diabetics because of renal disease still needs to be defined. Thus, it appears more likely that in diabetic cats, insulin resistance owing to renal disease plays a less important role than the reduced clearance of exogenous insulin caused by advancing renal disease and the associated increased potential for symptomatic hypoglycaemia.

It is unknown whether the lower maximum dose of detemir compared with glargine is related to impaired renal clearance or a higher molar potency in cats. In the initial clinical trials with detemir it was found that the molar potency of insulin detemir in humans was approximately a quarter of that of human insulin. In vivo studies in dogs and pigs found that detemir was equipotent to human insulin. In mice and rabbits (species traditionally used to determine the biological potency) detemir was six-fold less and greater than 15-fold less potent, respectively. The lower potency of detemir when compared with human insulin has been attributed to detemir's myristic acid moiety interfering with receptor binding, as well as possible differences in the binding to albumin. Owing to the observed differences between detemir and human insulin in humans, the manufacturer has defined 1 unit of insulin detemir to equal 24 nmol (1 unit of human insulin equals 6 nmol). For these reasons, detemir works approximately four-fold more potently in dogs than glargine.[28–30] As the study by Gilor et al, which compared detemir and glargine in healthy cats, did not find a difference in dosage effect, it appears less likely that the lower detemir dose required by this cohort is related to the receptor binding capacity of detemir, but, rather, it may be related to the high levels of renal disease observed in the cohort. Additional support for this hypothesis is that the incidence of biochemical and clinical hypoglycaemia was not different between the glargine- and detemir-treated cats, despite the same initial dose and subsequent dosing protocol being used.

Hence, an overall older cohort is more likely to have CKD and, thus, if, as in humans, this prolongs the half-life of insulin, a lower maximal dose may be required in these animals to produce equal levels of blood glucose control. Therefore, we wish to stress that the results of this study should not be viewed as a recommendation to treat diabetic cats with lower doses of insulin if they are treated with detemir instead of glargine.

In the past, the majority of popular German human glucometers reported blood glucose concentration in whole blood. However, these have been slowly replaced by plasma-equivalent type glucometers based on the recommendations of international panels of experts.[31] For example, in September 2009 and after our study was completed, all newly sold test strips for Roche's German Accu-Chek models became calibrated for plasma (and could still be used in older glucometers). In humans, the Accu-Chek plasma-calibrated glucometer measures 10–15% higher blood glucose concentrations when compared with the old whole blood calibrated meter according to the manufacturer.[32]

Repeated assessments of the accuracy of human portable blood glucose meters in cats and dogs demonstrated variability among the meters studied. In a feline study from the UK, all meters examined had the potential to under- and overestimate blood glucose levels to varying degrees throughout the glycaemic range.[33] In a canine study from the USA, neither of the two meters studied showed an exact agreement with the automated analyser, but the disagreement detected was thought not to lead to serious clinical consequences. The authors of the canine study recommended the use of the same device for monitoring trends in individual dogs and

using instrument-specific reference intervals.[34] In a further canine study from the USA, six glucometers showed substantial differences in accuracy.[35] Currently, there are no glucometers calibrated for feline blood and reading plasma-equivalent values available in Germany, but they are now available in USA and the UK (AlphaTRAK; Abbott Animal Health). The relatively low target blood glucose concentrations (2.8–5.5 mmol/l) used in our protocol reflect use of meters calibrated for humans and provide glucose measurement for whole blood. If our protocol is used with meters calibrated for feline blood which provide plasma-equivalent readings, the normal feline reference interval should be used as the target glucose range.

Conclusions

In conclusion, detemir, a low carbohydrate diet and a protocol for tight glycaemic control involving home monitoring results in high remission rates provided it is instituted within a median of 2 months after diagnosis. The incidence of CKD in cats with diabetes needs to be further investigated.

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Conflict of interest The authors do not have any potential conflicts of interest to declare.

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