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COMPARISON OF LENTE INSULIN AND NPH INSULIN THERAPY FOR THE TREATMENT OF NEWLY DIAGNOSED DIABETIC DOGS: A RANDOMISED STUDY

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Abstract

Clinical studies that compare Lente insulin and Neutral Protamine Hagedorn (NPH) insulin in diabetic dogs are lacking. This is a prospective, randomised, controlled clinical study aimed to compare the efficacy and safety of lente insulin and NPH insulin in diabetic dogs. Thirty client-owned, newly diagnosed diabetic dogs were included. Animals were randomised into two groups and received lente insulin or NPH insulin administered q12h. Follow-up re-evaluations were done at 1, 2, 4, 6, 8, and 12 weeks. At each re-evaluation, a physical exam, blood glucose curve (BGC), and serum fructosamine concentrations were performed. At the end of the study, the median insulin dose per injection was 0.61 U/kg (range, 0.34 to 0.92 U/kg) and 0.49 U/kg (range, 0.23 to 0.68 U/kg) in the lente and NPH groups, respectively. There was a significant improvement of polyuria and polydipsia and glucose concentrations in both groups. At the end of the study, the glycaemic control was considered good in 9/15 (60%) and 11/15 (73%) in the lente and NPH group, respectively. These differences were not significant. Lente insulin and NPH insulin were similarly effective in the treatment of dogs with DM.

Introduction

Various types of insulin are used to treat diabetes mellitus (DM) long-term.[1-8] Based on duration of action and potency, they include intermediate-acting (i.e. lente, Neutral Protamine Hagedorn [NPH]) and long-acting insulins (i.e. protamine zinc insulin [PZI], insulin glargine, and insulin detemir). Current guidelines for dogs with newly diagnosed DM recommend the use of insulin preparations with an intermediate duration of action.[9]

Lente is a porcine–origin zinc 40 U/mL insulin that consists of 35% short-acting amorphous insulin and 65% long-acting, microcrystalline insulin. Lente is approved by the Food and Drug Administration (FDA) for use in dogs and allows a good glycaemic control in most treated diabetic dogs.[3] NPH (100 U/mL) is recombinant human insulin, usually administered q12h. Some studies have demonstrated a good efficacy of this insulin in the treatment of canine DM.[1,4] One study observed that with NPH insulin, postprandial hyperglycaemia could occur in some well-regulated dogs.[4]

Several clinical studies evaluated single insulin products for the treatment of dogs with DM but clinical articles comparing the efficacy and safety of different insulin preparations are uncommonly reported in the veterinary literature. The aim of the present study is to compare the efficacy and safety of lente insulin and NPH insulin in newly diagnosed diabetic dogs.

Materials and Methods

Dogs

Thirty client-owned newly diagnosed diabetic dogs were prospectively enrolled in the study between November 2014 and September 2016. Dogs were recruited through the Teaching Hospital of the University of Bologna and three Italian private practices. Authors provided written instructions about diagnosis, treatment and monitoring of the disease to the practitioners involved in the study. Only one veterinarian in each recruiting center was responsible for the management of the dogs. DM was diagnosed based on clinical signs such as polyuria, polydipsia (pu/pd), weakness, weight loss, blood glucose concentration > 11 mmol/l after food had been withheld for at least 10 h, glucosuria, and serum fructosamine concentration > 340 μmol/L. To identify any concurrent disorders, complete blood count (CBC), serum biochemical profile, and complete urinalysis were performed at the time of enrollment in the study. Additional testing were done if clinically indicated. Dogs with a relevant concurrent disease (e.g., renal insufficiency, neoplasia, hypothyroidism, or hypercortisolism), that received insulin for > 7 days before admission and dogs that had received glucocorticoids or progestagens within the previous 60 days were not enrolled. Dogs with diabetic ketoacidosis (DKA) requiring aggressive management were used if their condition had been stabilized by medical treatment, including regular insulin therapy.

The recruitment of dogs in the study was voluntary and the only cost for the owner was the purchase of insulin, also the food was provided for free. The protocol and informed consent forms were approved by the Scientific Ethics Committee of the University of Bologna. All owners signed the written informed consent before enrollment in the study.

Study design

The trial was designed as a prospective, randomised, and controlled 3-month clinical study. Before treatment (day 0), anamnesis and physical examination were obtained as well as a CBC, serum biochemical profile (that included measurement of serum fructosamine concentration), and urinalysis were performed. At the time of diagnosis each dog was randomly assigned to receive lente insulin (Caninsulin, MSD, Boxmeer, The Netherlands) or NPH insulin (Humulin I, Eli Lilly Italia S.p.A., Sesto Fiorentino (FI), Italy). The randomisation was performed using a computer-generated randomisation program based on the Fisher–Yates shuffle algorithm. All dogs received the same prescription diet (Diabetic Royal Canin, © Royal Canin SAS, Milano, Italy), which was low in simple carbohydrates and high in

protein content. The diet was dry, canned, or a mixture of both based on the preferences of the dog. The diet and the formulation (dry/canned) were maintained for the entire duration of the study. The prescription diet was introduced as the dog's only food with a transition of 2–3 days from the dog's previous diet at the time of enrollment. Owners were instructed to feed dogs at the same time of insulin administration. The initial insulin dose for both products was 0.25–0.5 U/kg administered SC every 12 h. Six follow-up re-evaluations were performed 1, 2, 4, 6, 8, and 12 weeks after the initial evaluation. These evaluations included an assessment of clinical signs and determination of serum fructosamine concentration and BGCs. During each re-evaluation, food and insulin were given at home and blood glucose concentrations were measured after the dog arrived at the clinic (≤ 1 hour after insulin administration). To generate the blood glucose curves, blood capillary glucose was obtained from the pinna and was measured after 1, 2, 4, 6, 8, 10, and 12 h from insulin injection. The insulin dose was adjusted by 0.5 - 2U/dose at each evaluation, as required; the aim was to maintain blood glucose concentrations between 5 and 15 mmol/l. 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 hypoglycaemic episodes, body weight, and physical examination results), BGC, and serum fructosamine concentration. Hypoglycaemia was defined as blood glucose concentration < 4.4 mmol/l.

Analytical Methods

Blood glucose concentrations were measured in capillary blood obtained from the inner surface of the pinna using a hand-held glucometer produced for the dog (Glucocalea Wellionvet, Isomedic srl, (LO), Italy)[10]. Detectable blood glucose concentrations ranged from 1.1 to 33 mmol/l. When blood glucose concentrations were <1.1 mmol/l and >33 mmol/l, registered as "LO" and "HI" on the glucometer were arbitrary given a value of 1.1 mmol/l and 33 mmol/l, respectively. Fructosamine analyses were performed using a colorimetric nitroblue tetrazolium reduction method (Fructosamine, Olimpus, Milano, Italy). The intra- and interassay coefficient of variation (CV) for serum fructosamine were 4.1% and 2.5%, respectively. The sensitivity of the assay was 5 µmol/L. CBC (Advia 2120 Hematology System, Siemens Healthcare Diagnostics. Tarrytown, NY), serum biochemical profiles (AU2700 Beckman-Coulter/Olympus, O'Callaghan's Mills, Ireland) including lipase (1,2□diglyceride enzymatic/colorimetric assay)(Lipase, OSR 6130, Olympus/Beckman Coulter, Lismeehan O'Callaghan's Mills, Co. Clare Ireland) and urinalyses were performed by standard laboratory methods in a reference laboratory (Mylav Laboratorio Lavallonea, Alessano, Italy).

Assessment of Efficacy

In order to objectively evaluate the glycaemic control, the following parameters were used: body weight, presence of polyuria/polydipsia, median glucose of the BGC, blood glucose nadir of the BGC, overall evaluation of the BGC, and serum fructosamine concentration. For each parameter, a score was arbitrarily assigned: 2 = good, 1 = moderate, and 0 = poor. Maintaining or increases of body weight was considered good (score = 2), conversely a decrease (> 5%) of the body weight was judged as poor (score = 0). In obese dogs, the weight loss needed to obtain an optimal BCS was not considered as negative in the scoring system. In such dogs, even if they were losing weight a score of 2 was given. Absent, improved, and present/unchanged-present/worsen pu/pd was considered good (score = 2), moderate (score = 1), and poor (score = 0), respectively. Median glucose of the BGC < 12.7 mmol/l, between 12.7–16.6 mmol/l, and > 16.6 mmol/l was considered good (score = 2), moderate (score = 1), and poor (score = 0), respectively. Glucose nadir of the BGC was considered good (score = 2), moderate (score = 1), and poor (score = 0), if it was < 10 mmol/l, between 10.0–13.9 mmol/l, and >13.9 mmol/l, respectively. The overall evaluation of the BGC was considered good (score = 2) if ≥50% of blood glucose measurements were between 4.4–15.0 mmol/l or poor (score = 0) if < 50% of the glucose measurements were between 4.4–15 mmol/l. Serum fructosamine concentration < 450 µmol/L, between 450–550 µmol/L, and > 550 µmol/L were considered good (score = 2), moderate (score = 1), and poor (score = 0), respectively.

A total clinical score between 0 and 12 was obtained adding all the scores. A total clinical score between 8–12, 4–7, and 0–3 points was suggestive of good, moderate, and poor glycaemic control, respectively.

Data Analysis

Statistical analysis was performed with commercially available software (Prism version 5.0d, GraphPad software Inc, San Diego, Calif.).

The distribution of data was assessed by using the D'Agostino and Pearson tests. The parameters normally distributed were expressed as mean ± SD, while the data without a normal distribution were expressed as median (minimum and maximum value). Proportions and percentages were used to describe categorical variables. Parametric and non-parametric tests were used to analyze data based on the distribution. Categorical variables were compared using the Fisher's exact test. Differences between groups for age, body weight, laboratory results, and insulin dose, recorded at admission and body weight, laboratory results, and insulin dose over the 3 months study period were analyzed using the Mann-Whitney U-test or t-test. Within each group, differences in body weight, insulin dose, blood glucose, and fructosamine concentrations between baseline or first re-evaluation and the end of the study were evaluated using the Wilcoxon signed rank test or paired t-test. Differences were considered significant at $P < .05$.

Results

Thirty dogs were enrolled in this study. Fifteen dogs were treated with lente insulin and 15 with NPH insulin. Mean age was 9.6 years (SD, ± 1.9 years). There were 17 mixed-breed dogs, 5 English Setters, 3 Labrador Retrievers, 2 Yorkshire Terriers, 1 Maltese, 1 Cocker Spaniel, and 1 Yugoslavian Shepherd Dog. Thirteen were spayed females, 3 intact females, 5 neutered males, and 9 intact males. All 3 intact female dogs were spayed within 4 weeks after inclusion in the study. Median body weight was 17.8 kg (range, 4.2 to 59.8 kg). At the time of the enrollment no significant differences between dogs assigned to lente or NPH group considering age, sex, or body weight were observed (Table 1). Six dogs were enrolled after resolution of DKA, 3 were in the lente insulin group, and 3 in the NPH insulin group. No differences considering serum glucose and fructosamine concentrations at the time of enrollment in the study between the two groups were detected (Table 1). All dogs accepted the new diet and in all subjects it was maintained throughout the study. Of the expected 180 follow-up re-evaluations (30 dogs for 6 follow up re-evaluations) only 170 were performed. 10 re-evaluations were lost because owners did not come to the clinic, i.e. skipped the appointment. Two dogs lost 2 re-evaluations and 6 dogs lost one re-evaluation. The last re-evaluation (at the 3rd month) was performed on all animals. Mean insulin dosages per injection at the beginning and at the end of the study were 0.36±0.08 U/kg and 0.6 ± 0.14 U/kg in lente group and 0.32± 0.07 U/kg and 0.47±0.14 U/kg in dogs treated with NPH insulin. The increase of the insulin dose throughout the study was significant in both groups and at the end of the study the insulin dose was significantly lower in the NPH group when compared to the lente group ($P = 0.0206$).

Blood glucose concentrations < 4.4 mmol/l were identified in 3/86 (3.5%) and 6/84 (7.1%) of total BGCs performed by dogs treated with lente and NPH insulin, respectively. Such difference was not significant. Symptomatic hypoglycemia was not recorded in both groups and no reactions at the site of insulin administration were reported.

Evaluating all the BGCs, the glucose nadir was observed more commonly 4-6 h and 2-4 h after insulin injection in the lente group and in the NPH group, respectively (Figure 1).

Throughout the study, body weight did not change significantly either in the lente group ($P = 0.85$) nor in the NPH group ($P = 0.95$). Median blood glucose concentrations of the BGCs at the end of the study, compared with the first re-evaluation (1 week), were significantly decreased in both groups: from 23.0 mmol/l (range, 9.6–29.6) to 13.9 mmol/l

(range, 5.0–22.6) in the lente group (P=0.009); and from 19.8 mmol/l (7.8–28.1) to 11.7 mmol/l (4.6–23.2) in the NPH group (P = 0.04). Serum fructosamine concentrations at the end of the study were significantly decreased compared with the evaluation before treatment only in the group treated with NPH insulin: from 607 µmol/L (288–880) to 418 µmol/L (292–848) in the NPH group (P = 0.005); and from 455 µmol/L (224–849) to 457 µmol/L (329–749) in the lente group (0.854).

Table 2 reports the assessment of the glycaemic control in the 2 groups at the end of the study and considers body weight, polyuria-polydipsia, median blood glucose concentration of the BGCs, blood glucose nadir, overall evaluation of the BGCs, and the serum fructosamine concentrations.

At the end of the study, the glycaemic control as evaluated using the total clinical score was classified as good in 9/15 (60%), moderate in 3/15 (20%), and poor in 3/15 (20%) dogs treated with lente insulin. In the group treated with NPH insulin, the glycaemic control was classified as good in 11/15 (73%), moderate in 4/15 (27%), and poor in 0/15 (0%) of dogs. Such differences between the two groups were not statistically significant. In the 4 dogs treated with NPH insulin that at the end of the study had a moderate glycaemic control this was apparently not due to short insulin duration but rather to insufficient glycaemic suppression (nadir >13.9 mmol/l).

The 3 dogs included after the resolution of DKA in the lente group at the end of the study were classified with good (n=2) or moderate (n=1) glycaemic control, respectively. The 3 dogs included after the resolution of DKA in the NPH group at the end of the study were all classified with moderate glycaemic control. None of the dogs included in the study showed clinical signs (e.g. vomiting, painful abdomen at the physical examination, diarrhea) consistent with pancreatitis. In the group treated with lente insulin serum lipase activity resulted above the reference range in 4/15 dogs at T0 and in 4/15 dogs at T12. In the group treated with NPH insulin 7/15 dogs at T0 and 4/15 dogs at T12 had serum lipase activity above the reference range. In the group treated with lente insulin the 3 dogs classified at the end of the study with moderate glycaemic control had lipase activity above the reference range in 2/7, 1/7 and 0/7 re-evaluations, respectively and the 3 dogs classified with poor glycaemic control had lipase activity above reference range in 5/7, 1/7 and 5/7 re-evaluations, respectively. In the group treated with NPH insulin the 4 dogs classified with moderate glycaemic control had lipase above reference range in 3/7, 0/7, 1/7 and 1/6 re-evaluations, respectively.

Discussion

The results of this study indicate that both lente and NPH insulin are safe and efficacious as treatment for dogs with newly diagnosed DM.

Starting insulin dosage in the lente and NPH groups, according to the treatment protocol, were commonly reported in the veterinary literature.[11] At the end of the study, insulin dosage observed in both groups was similar to what was obtained in previous studies that evaluated lente and NPH insulin in dogs.[3,1] Mean insulin dose after three months of treatment was significantly different between the lente and NPH groups, this is likely related to the greater potency of NPH insulin. Median blood glucose concentrations were significantly reduced after three months of insulin treatment in both groups; whereas the median fructosamine concentration was significantly reduced only in dogs treated with NPH insulin. This finding must be interpreted with caution because at time of enrollment, despite not significant (P = 0.08), the median fructosamine concentration was higher in the NPH group (607 µmol/L) than in the lente group (455 µmol/L), which was already a value closer to the normal reference range. Blood glucose nadir was identified mostly at 2 and 4 h from the insulin administration in dogs treated with NPH insulin and at 4 and 6 h in dogs treated with lente insulin. These results are similar to those obtained in other studies where time to nadir in dogs treated with NPH insulin resulted at 2, 5, and 4.9 h [12,13,4] and from 4–8 h in dogs treated with lente insulin.[14]

In the NPH group, three of the four dogs classified as having a moderate glycaemic control at the end of the study, were enrolled after resolution of DKA. There is no evidence to support that dogs after the resolution of DKA are more difficult to control as diabetic patients. However, it is possible that, despite the complete diagnostic work-up before enrolment, such dogs had an insulin resistance for not clarified reasons (e.g. undiagnosed disease such as subclinical pancreatitis). In both groups no clinical signs consistent with acute pancreatitis were observed; however, the presence of mild acute pancreatitis or chronic pancreatitis cannot be excluded. The diagnosis of chronic pancreatitis can be very challenging because of the nonspecific and often low-grade nature of the clinical signs and the relatively low sensitivity of non-invasive diagnostic tests.[15] At the time of diagnosis no differences in terms of serum lipase activity between the two groups was observed. Two of 3 dogs treated with lente insulin and classified with poor glycaemic control showed serum lipase activity above the reference range in most of the re-evaluations. In these dogs a chronic pancreatitis as a cause of insulin resistance cannot be excluded. A limitation of the present study was that serum lipase activity was determined using the 1,2diglyceride enzymatic/colorimetric assay and not the canine pancreatic lipase immunoreactivity that seems to have higher sensitivity in detecting chronic pancreatitis.[16] However, the present study is focused on the comparison of the efficacy and safety of two different insulin products, rather than evaluating the possible causes of insulin resistance.

In terms of hypoglycaemic events, this study obtained better results in comparison with other studies evaluating lente and NPH insulin. In a study performed on 53 dogs treated with lente insulin, clinical hypoglycaemic events were reported in 38.6% of patients with total of 24 events (15%) with glucose concentration < 3.3 mmol/l on 159 BGCs. One possible reason for the high incidence of hypoglycemia was a starting insulin dosage that was high, > 1 U/kg every 24 h; in such a study, 41% of dogs enrolled had necessity for insulin dose reduction.[3] Another study performed on dogs treated with NPH insulin showed clinical hypoglycemia in 4 dogs of 57 (7%).[1] The low incidence of hypoglycaemic episodes observed in the present study is probably related to low starting insulin doses (0.25–0.5 U/kg twice daily), frequent re-evaluations, and consequent frequent dosage adjustments.

All dogs have been fed with the same diet for the entire length of the study, which minimized food dependent glycaemic variability. In contrast to similar studies[1-8], only newly diagnosed diabetic dogs were enrolled. This is in accordance with the study's aim to compare two insulin treatment options to investigate if one of the two was more effective and/or safe as a first-line treatment. In this study, the residual endogenous insulin secretion has not been tested. Likely, some of the included dogs had some insulin production, i.e. the so-called "honeymoon period", and this could have partially influenced the results of this study.

The main limitation of the present study, similarly to other clinical veterinary studies on DM, was the small number of dogs included. This has been a limit in terms of reaching significance when comparing results between the two groups. For example, at the end of the study, glycaemic control was classified as good in 11/15 (73%) dogs treated with NPH insulin and in 9/15 (60%) dogs treated with lente insulin; however, such differences were not significant. According to the calculation of statistical power and sample size and assuming the same percentages of glycaemic control, 136 instead of 15 dogs in each group would have been necessary to achieve statistical significance.

Some authors consider NPH insulin a second choice in comparison with lente insulin[17]; this is due to a study performed on 10 diabetic dogs in which duration of insulin action was too short.[4] That study evaluated the serum insulin and glucose concentrations for a period of 10 h from insulin administration. In four dogs, the insulin duration of action at the end of the study was 5.5 h; in another four dogs the duration was longer than 10 h; and in the remaining two dogs, it was not possible to evaluate insulin duration of action because there was not enough blood glucose concentration reduction to assess the duration of action. The authors of that study concluded that more investigations are needed to

assess the real duration of action for NPH insulin.[4] This study did not to evaluate NPH insulin's duration of action; however, we observed for dogs in the NPH group that moderate glycaemic control was not related to the short duration of insulin action.

Both lente and NPH insulin have demonstrated safety and efficacy in the treatment of dogs with uncomplicated DM. In general, dogs with NPH insulin obtained a higher percentage of better glycaemic control; although these differences were mostly not significant. The low incidences of hypoglycaemic events were likely obtained because of low insulin starting doses that were gradually increased and frequent re-evaluations. According to this study, NPH and lente insulin can be considered similarly effective for the treatment of uncomplicated DM in dogs.

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Figure 1. Histograms indicate the number of blood glucose curves (%) from dogs with diabetes mellitus treated by administration of lente insulin (n = 15) or Neutral Protamine Hagedorn (NPH) insulin (n = 15) twice daily for 3 months where the glucose nadir was observed at 1 or 2, 4, 6, 8, 10, and 12 h after insulin injection, respectively

Table 1 Baseline characteristics of 30 dogs included in the study

Variable	**Lente Group**	**NPH Group**	***P* Value**
N° of Dogs	15	15	
Female	8 (1 intact, 7 spayed)	8 (2 intact, 6 spayed)	1
Male	7 (4 intact, 3 neutered)	7 (5 intact, 2 neutered)	1
Age (years)	9 (6–12)	10 (7–13)	0.35
Body weight (Kg)	12.5 (4.2–59.8)	16.0 (4.4–50.0)	0.60
Serum glucose (mmol/l)	22.2 (3.6–34)	21.3 (7.3–45.8)	0.69
Serum fructosamine (µmol/L)	455 (224–849)	607 (288–880)	0.08
Serum lipase activity (IU/l)	373 (179-2795)	410 (107-1343)	0.79

Table 2. Assessment of the glycaemic control using different parameters in 30 diabetic dogs treated for 3 months (results at the end of the study) with lente insulin (n = 15) or NPH insulin (n = 15). BCG = blood glucose curve

Method of assessment	**Score**	**Lente Group**	**NPH Group**	***P* value**
Body weight	Good	13/15 (87%)	15/15 (100%)	0.80
	Poor	2/15 (13%)	0/15 (0%)	0.49
Polyuria-polydipsia	Good	10/15 (67%)	13/15 (87%)	0.78
	Moderate	1/15 (7%)	2/15 (13%)	1.00
	Poor	4/15 (27%)	0/15 (0%)	0.11
Median blood glucose concentration (BGC)	Good	7/15 (47%)	9/15 (60%)	0.76
	Moderate	3/15 (20%)	3/15 (20%)	1.00
	Poor	5/15 (33%)	3/15 (20%)	0.70
Glucose nadir (BGC)	Good	8/15 (53%)	10/15 (67%)	0.77
	Moderate	3/15 (20%)	3/15 (20%)	1.00
	Poor	4/15 (27%)	2/15 (13%)	0.66
Overall evaluation of the blood glucose curve	Good	9/15 (60%)	11/15 (73%)	0.78
	Poor	6/15 (40%)	4/15 (27%)	0.72
Serum fructosamine concentration	Good	6/14 (43%)	10/15 (67%)	0.54
	Moderate	4/14 (29%)	3/15 (20%)	1.00
	Poor	4/14 (29%)	2/15 (13%)	0.66