The Journal of Veterinary Medical Science

NOTE

Internal Medicine

The effect of Insulin Degludec on glycemic control in diabetic cats over a 12-month period

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J. Vet. Med. Sci.
82(6): 695–698, 2020
doi: 10.1292/jvms.19-0309

Received: 9 June 2019
Accepted: 6 April 2020
Advanced Epub:
20 April 2020

ABSTRACT. Insulin degludec (IDeg) is a long-acting basal insulin recently developed for use in humans. This study aimed to investigate the effects of IDeg on glycemic control in diabetic cats. Changes in body weight, IDeg dosage, and glycated albumin (GA) were evaluated at 0, 1, 3, 6, 9, and 12 months following initiation of IDeg. A significant decrease in GA was observed and a mean GA level below 25% was achieved between 3 and 12 months. Furthermore, a significant increase in body weight was observed between 3 and 12 months. The mean IDeg dose was 0.75 ± 0.68 IU/kg/day at 12 months. Taken together, long-term glycemic control was successfully achieved in diabetic cats using IDeg.

KEY WORDS: diabetes, feline, glucose lowering effect, ultra-long-acting insulin

Insulin degludec (IDeg) is a new basal form of insulin that generates soluble multihexamers following subcutaneous injection, resulting in an exceptionally long duration of action (>42 hr), thus effectively reducing blood glucose levels in individuals with diabetes mellitus [17, 19, 21]. In human studies, the half-life of IDeg is longer than that of insulin glargine following subcutaneous administration (25 vs. 12 hr, respectively) [3–5].

There has been a marked increase in the number of cats with diabetes mellitus (DM) [6]. Currently, diabetic cats are treated with insulin injections, oral hypoglycemic drugs, and/or prescription diets [2]; however, diabetic cats with severe hyperglycemia (>350–500 mg/d*l*) generally require daily insulin administration [7]. Protamine zinc insulin is the current gold standard for the treatment of feline diabetes in Japan as it is the only commercially available insulin for cats in this region. Furthermore, long-acting human insulins, including insulin glargine and insulin detemir, are often used in the long-term management of feline diabetes [1, 2, 13]. Previously, a clear difference among four different insulin preparations for dogs was demonstrated by examining their time-action profiles [9, 14, 18]. The action of IDeg was persistent for >20 hr, representing its long profile [14] as well as insulin detemir (IDet), and insulin glargine (IGla) [9, 14, 18]. However, the effects of IDeg have not yet been investigated in cats; therefore, in the current study, the effects of IDeg upon long-term glycemic control in diabetic cats were studied.

Eight cats with DM brought to the Nippon Veterinary and Life Science University Veterinary Medical Teaching Hospital from April 2016 to April 2018 were monitored for 12 months of IDeg treatment. The profiles of the eight cats are presented in Table 1. All diabetic cats were defined by clinical signs (polyuria and polydipsia) and the documentation of persistent fasting hyperglycemia (>250 mg/d*l*), over 20% glycated albumin (GA) and glucosuria. A serum GA of over 20% was considered abnormal and a normal reference range of GA was 7.5–13.9% for GA (%) (95% C.I.) in normal healthy cats [8]. Five of the eight cats were newly diagnosed as diabetic and had not had insulin administered prior to this investigation. The remaining three cats were previously diagnosed and had been treated with insulin prior to this investigation (Table 1). However, as these three cats had fair to poor glycemic control (GA; cat 1 for 28%, cat 7 for 30% and cat 8 for 33%), changing their insulin preparation was allowed by the owners. Informed consent was obtained from the owners following the review of the purpose, nature, potential risks, and benefits of the study. All cats were injected with IDeg (Tresiba, Novo Nordisk Pharma Ltd., Tokyo, Japan) once or twice daily with dietary feeding twice daily. The initial dosages administered to the previously untreated diabetic cats were 0.5–2.0 units/cat/once or twice a day depending upon clinical signs and GA levels. These doses were adjusted throughout the treatment period according to the clinical condition of each individual (such as improvement in polyuria/polydipsia and increasing body weight) and the serum GA level for maintaining 11.9–25.6% (between excellent to fair glycemic control) [8]. The cats were fed individual diets by their respective owners, which provided a daily calorie intake of 0.8–1.6 × resting energy requirement (Ideal Body Weight$^{0.75}$ × 70). Feeds were provided twice daily. Owners were educated on the potential complications of this investigation, which included

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Table 1. Profile of diabetic cats used in the current study

No.	Breeds	Age (Years)	Sex	Body weight (kg)	Food	Previous type and dose of insulin (Units/kg/day)	2 hr blood glucose monitoring	Concurrent disease and medication
1	Mix	16	Castrated male	4.8	Diabetic dry (RoyalCanin)	0.91 (insulin glargine)	○	None
2	Mix	13	Castrated male	5.9	Renal dry, Fibre response dry (RoyalCanin)	—	—	None
3	Mix	11	Spayed female	3.2	Diabetic dry (RoyalCanin)	—	—	None
4	Mix	9	Spayed female	3.4	Diabetic dry (RoyalCanin)	—	○	None
5	Japanese Bobtail	8	Castrated male	3.2	Commercially available dry	—	—	None
6	Mix	8	Spayed female	4.4	Diabetic dry (RoyalCanin)	—	○	None
7	Mix	6	Castrated male	4.5	Diabetic dry (RoyalCanin)	0.27 (insulin detemir)	○	None
8	Mix	4	Spayed female	4.6	Commercially available dry	0.43 (insulin detemir)	—	None

hypoglycemia, and were encouraged to remain in close contact with the authors throughout the study period.

For GA measurement, blood samples were obtained from the peripheral vein of each cat at 0, 1, 3, 6, 9, and 12 months after the initial IDeg treatment. In order to evaluate the effect of IDeg on glucose concentration, glucose concentration measurements were taken every 2 hr in four of eight diabetic cats (Cats 1, 4, 6, 7) at 1, 3, 6, 9, and 12 months. These animals were admitted to the veterinary hospital for one-half day in order to complete these measurements. Preprandial blood sampling was performed from the peripheral vein of each cat (0) and at 2-hr intervals after feeding, with insulin injections between 0 and 10 hr. Blood samples for measuring GA levels were collected in polypropylene tubes and allowed to clot at 20 ± 5°C for 10 min. After clotting, blood samples were centrifuged immediately at 1,700 × *g* for 10 min at 4°C in order to obtain serum samples. Samples were immediately analyzed. Serum GA levels were measured using a commercial kit (Lucica GA-L; Asahikasei Pharma Co., Tokyo, Japan, ALB II-HA test WAKO; Wako Pure Chemical Co., Ltd., Osaka, Japan) and an autoanalyzer (Type 7180 Automatic Analyzer; Hitachi High-Technologies Co., Ltd., Tokyo, Japan). Glucose concentrations were measured using the veterinary portable blood glucose meter (The BS-7110, Arkray Co., Ltd., Kyoto, Japan). This work was approved by the Nippon Veterinary and Life Science University Animal Research Committee (Acceptance Number: 27S-57).

Data are presented as mean ± standard deviation (SD). Statistical significance was determined using one-way or two-way repeated measures (RM) ANOVA and Dunnett's *post-hoc* test using GraphPad Prism 5 analysis software (GraphPad Software, Inc., San Diego, CA, USA). Differences were considered significant at values of $P<0.05$.

Significant decreases in GA were observed during treatment with IDeg ($P<0.05$, one-way RM ANOVA), with lower levels being recorded at 6, 9, and 12 months relative to the pretreatment level ($P<0.05$, Dunnett's *post-hoc* test) (Fig. 1A). The changes in the mean GA levels were 30.3 (before IDeg treatment), 25.6, 23.0, 18.5, 17.6, and 19.1% at 0, 1, 3, 6, 9, and 12 months, respectively. Moreover, a significant increase in body weight was observed following IDeg treatment ($P<0.05$, one-way RM ANOVA), with higher levels being recorded at 3, 6, 9, and 12 months than at 0 months ($P<0.05$, Dunnett's *post-hoc* test) (Fig. 1B). Following long-term IDeg treatment, the mean body weight after 12 months was ~28% greater than pretreatment (mean ± SD; 5.4 ± 1.08 versus 4.2 ± 0.94). The insulin dose did not change significantly over the treatment period (one-way RM ANOVA) (Fig. 1C). IDeg had no significant effect on temporal glucose concentration at any time between 1 month and 12 months in four diabetic cats (two-way RM ANOVA) (Fig. 2). Additionally, no significant difference was observed in the mean glucose $AUC_{0\text{-}10hr}$ between 1 month and 12 months in four diabetic cats (Fig. 2 inset) (one-way RM ANOVA). A single hypoglycemic event occurred in one diabetic cat. The cat displayed mild signs, which consisted of trembling and sialorrhea. Clinical hypoglycemia occurred at 1.04% for one month during the 12-month study period.

IDeg is an ultra-long-acting insulin preparation associated with a reduced risk of hypoglycemia, according to human studies [1, 20]. As cats are of a carnivorous origin, they consume diets that are high in protein and low in carbohydrates; thus, an indistinct peak of postprandial insulin secretion is usually observed [10–12]. Furthermore, small and frequent food intake is common in feline populations; thereby, continual, long-acting insulin is important for maintaining euglycemia and a healthy status. As such, IDeg was considered as a suitable treatment for diabetes mellitus in cats as it mimics a postprandial physiological insulin secretion pattern. In the current study, a reduction in GA levels was observed along with improvement in the clinical sign in diabetic cats following IDeg treatment. Furthermore, a mean GA level was achieved, falling below 25%, for the 3 to 12 months of treatment. Temporal glucose concentrations measured at 2 hourly intervals, and mean glucose $AUC_{0\text{-}10hr}$ between 1 month and 12 months in 4 diabetic cats did not show any significant differences; however, mean glucose $AUC_{0\text{-}10hr}$ gradually decreased as follows: 2,604, 2,492, 2,202, 1,991, and 2,032 for 1, 3, 6, 9, and 12 months, respectively. As such, the reduction of GA levels and the gradually decreasing mean glucose

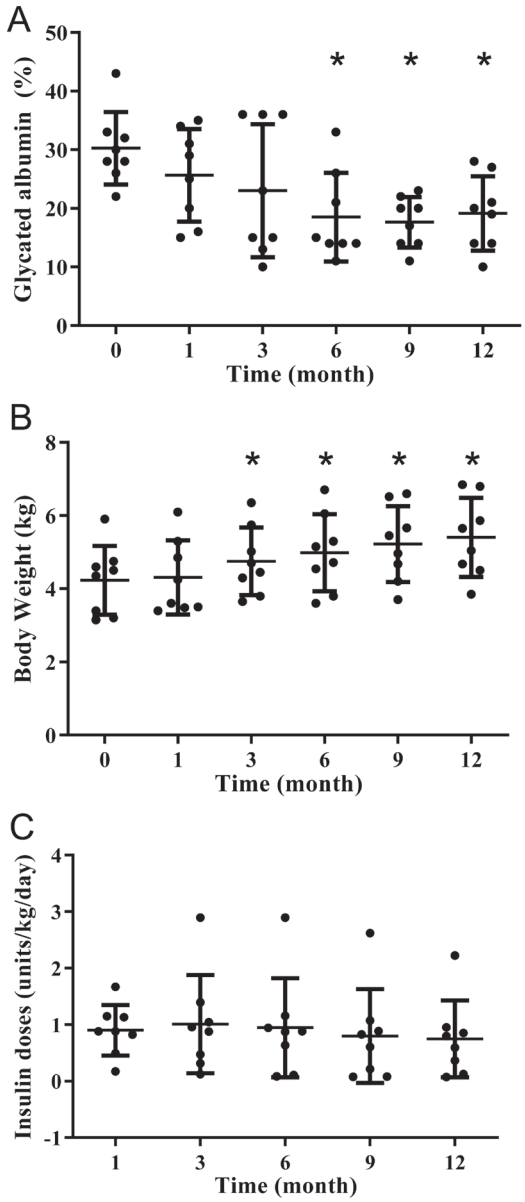

Fig. 1. Change in glycated albumin (a), body weight (b) and insulin doses of Insulin degludec (c) in eight diabetic cats throughout 12 months of Insulin degludec treatment. Values are expressed as plot and mean ± SD. Asterisks indicate significant differences (P<0.05) as compared with the 0-month value for glycated albumin and body weight.

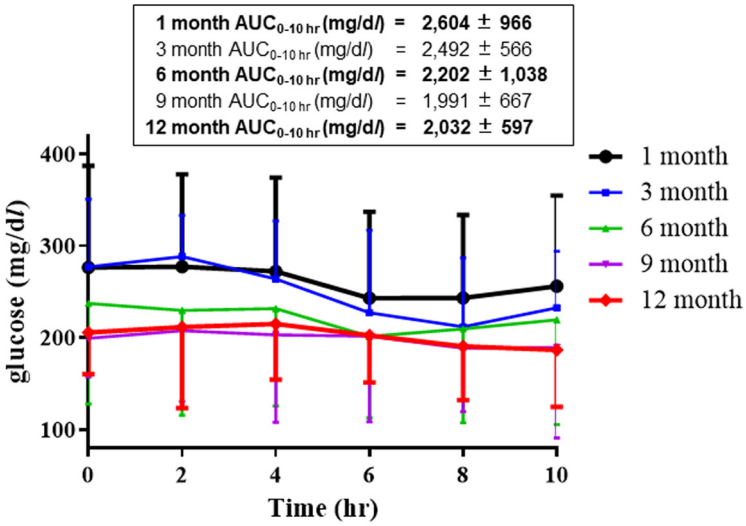

Fig. 2. Comparison of temporal glucose concentrations at 2-hr intervals in four diabetic cats after insulin degludec treatment at 1, 3, 6, 9, and 12 months. Values are expressed as mean ± SD. Inset indicates the total area under the curve (0–12 hr) (mean ± SD) at 1, 3, 6, 9, and 12 months.

$AUC_{0\text{-}10hr}$ suggest that injection of IDeg led to a successful long term treatment. Furthermore, temporal mean glucose concentrations between 0 and 10 hr in four diabetic cats suggested that IDeg induced continuous glucose-lowering effect without any pronounced peak effect, and indistinct peak effect was observed between 8 and 10 hr. Therefore, veterinary clinicians should be aware of hypoglycemic events between 8 and 12 hr after IDeg injection. Diabetic cats were treated with a mean dose of IDeg at 0.75 [min-max: 0.07–2.22] units/kg/day at 12 months. In previous studies, there was a clear difference in mean insulin dosage among ProZinc, IGla, and IDet [13, 15, 16]. According to previous studies, injected doses (mean [min−max]) were 0.59 [0.1–1.04], 0.43 [0.12–1.0], and 0.62 [0.07–0.95] units/kg/day for ProZinc, IGla, and IDet, respectively. Although it is difficult to compare results (due to differences in the protocol and in the diabetic cats studied), relatively higher doses of IDeg may be required for the treatment of diabetic cats when compared to other insulin preparations. The monthly incidence rate of hypoglycemic events during treatment with ProZinc, IGla, and IDet was reported as 1.0%, 0.3%, and 0.9%, which was not significantly different [13, 15, 16]. The incidence rate of clinical hypoglycemia was 1.04% for one month using IDeg in the current study; however, only eight diabetic cats were included in this investigation, which is too small a sample to accurately assess the incidence rate of hypoglycemic events.

The low statistical power of the results, attributed to the small sample size, is the primary limitation of this investigation. Due to the vast biological variability between animals, the sample number used in this study was too small to accurately assess glycemic control (e.g., GA). Despite this, GA can provide an index of glycemic control for the previous 1–3 weeks and can be used as a substitute for the evaluation of fructosamine concentration in cats [8]. Therefore, the effect of IDeg using GA as a glycemic control marker was calculated.

In conclusion, long-term IDeg treatments increased the body weight of diabetic cats and were effective in the amelioration of glycemic control. Therefore, IDeg is an effective insulin preparation for the management of diabetes in cats.

CONFLICT OF INTEREST. No potential conflict of interest was reported by the author.

ACKNOWLEDGMENTS. This work was supported by JSPS KAKENHI [Grant Number 17K08112]. The funding agency had no role in the study design, the collection, analysis, or interpretation of data, the writing of the report, or the decision to submit the article for publication.

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