INSULIN CHOICE AND TREATMENT PROTOCOL FOR "HEALTHY" DIABETIC FELINES

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Abstract:*Demand of exogenous insulin administration is currently limited by a series of factors, such as unbalanced pharmacodynamics, low therapeutic index, inconsistent intensity of effect, high physical instability and need for administration by injection. Still, the broad panel of insulin analogues available at the moment has a vital role in the treatment of diabetes mellitus, allowing individualized glycemic control in diabetic cats.*

The current paper describes the specific treatment protocol for clinically stable diabetic felines, focusing on two types of insulin frequently used in Romania,.

Data were collected from the medical records of cats presented at the veterinary teaching hospital of Faculty of Veterinary Medicine of Iasi, Romania. Cases were considered eligible for inclusion in the study if registered with a clear diagnosis of DM and were in a stable clinical condition. Therapeutic protocol focusing on dosing regiments for clinically stable diabetic cats, included two commercially available preparations: glargine and premixed isophane insulin. All cats were treated with both types of insulins and therapy was further continued with the preparation that provided the ideal control of blood glucose level.

Diabetes mellitus was diagnosed in 65 cats, of which only 18 were in a stable clinical condition. In 15 cats, ideal control was obtained with insulin glargine, with a median dose of 0.6 IU/kg (range: 0.2-1.1 IU/kg) administered twice daily. Only 3 cases were managed long term with 0.8 IU/kg (0.4-1.9IU/kg) premixed isophane twice daily. The premixed insulin never exceeded a period of action of 8 hours and allowed reinstallation of hyperglycemia on a time interval varying from 2 to 4 hours before the next administration.

Insulin glargine provided a good control of blood glucose level, with a very low incidence of subclinical hypoglycaemia episodes and was associated with a higher remission rate of diabetes. Premixed isophane insulin was associated with a blood glucose level to the lower normal range and with frequent hypoglycemia episodes. Also, due to the accelerated metabolism, isophane insulin activity did not reach the second administration in the day, thus cats were hyperglycemic for a varying length of time during the day.

Keywords: *feline diabetes, glargine, hyperglycaemia, insulin treatment, isophane,.*

INTRODUCTION

With an impressive body of research developed until present on diabetes mellitus (DM), specific treatment still relies on exogenous injectable insulin administration. Development and biosynthesis of recombinant DNA insulin analogs has provided various types of preparations, each with different pharmacokinetics, which allow adequate control of both basal and prandial glycemia. Recombinant DNA insulin analogs are defined as artificially modified forms of insulin, with different sequentiality and pharmacokinetics from natural endogenous insulin. For each type of insulin the hypoglycemiant effect, action onset and length of activity are different from one to another. Insulin analogues can be of bovine, porcine, or human synthesis, replicated on non-pathogenic bacterial or fungal cultures. Bovine insulin shares the highest degree of similarity with the feline insulin, with only a single amino acid variation on position 18 of chain A. Unfortunately, bovine preparations are

no longer available on the market and insulin treatment generally relies on either artificial, porcine or human insulin (Mooney and Peterson 2012). Compared to the human form, endogenous feline insulin presents variations on four amino acids, the former sharing more similarities with canine insulin, with a single variation on the last amino acid of the B chain (Lehninger 1982). Although the broad panel of insulin analogues available at the moment allows individualized glycemic control, insulin still remains a difficult to handle hormone. Its exogenous demand is limited by a number of factors, such as unbalanced pharmacodynamics, low therapeutic index, inconsistent intensity of effect, high physical instability and the need for administration by injection (Mayer, Zhang et al. 2007).

In cats, the purpose of insulin treatment generally targets bringing blood glucose levels below the renal threshold (<270 mg/dl) and maintain close to normal parameters for as long as possible during the day and between insulin doses. Insulin treatment is aimed at eliminating the toxic effect generated by high blood glucose (glucotoxicity) and remission of polyuria and polydipsia syndrome (PU/PD). In some cases, depending on the causal agent (obesity, iatrogenic diabetes mellitus and other associated diseases), an adequate insulin treatment protocol, can achieve DM remission. Briefly, remission can be translated as the resumption of pancreatic β cells secretory capacity, followed by total withdraw of the need for exogenous administration of insulin, with the possibility of relapse when causal agents reoccur.

The current paper describes the ideal administration protocol of two types of insulin frequently used in Romania for the therapy of feline DM, focusing on insulin dosing, type and regiments for clinically stable diabetic cats.

MATERIALS AND METHODS

Data was collected from the medical records of cats presented at the veterinary teaching hospital of Faculty of Veterinary Medicine of Iasi, Romania. Case registration revised the medical records of both male and female cats, with ages 4 weeks to 18 years. Cats were considered eligible for inclusion in the study if registered with characteristic clinical signs and a clear diagnosis of DM (Ettinger and Feldman 2005, Gunn-Moore 2005). Diagnosis was based on the clinical signs of PU/PD, polyphagia associated with weight loss, persistent fasting hyperglycemia over 270 mg/dl (80-120 mg/dl), glycosuria and data obtained on the general serum biochemistry (Blois, Dickie et al. 2010, Reusch 2011, Solcan 2011). Only cats in a stable clinical condition, without pre-renal azotaemia, non-ketotic and with a normal appetite, were considered eligible for the study. Therapeutic protocol included two commercially available preparations: synthetic long acting insulin glargine and a human origin premixed short and intermediate acting form, containing 70% human isophane insulin and 30% human soluble insulin. All cats were treated with both types of insulins and continued on the type of insulin that provided the ideal control of blood glucose level.

Insulin type and dose were administered according to the patient's clinical condition and physical characteristics. For both glargine and premixed preparations, dosing was started with 0.2 IU/kg/12 and increased gradually, with variations of 0.2/kg/dose. The new dose was maintained unaltered for a period of three to five days before further modifications (Jacquie Rand 2004), in order to balance insulin action and avert overlap. Dose reductions were preformed according the imminence of hypoglycemic crisis, varying from 30% to 50%

reduction. In cases where blood glucose level decreased below 40 mg/dl, insulin administration was withhold completely until clinically and biochemically stable (Ettinger and Feldman 2005, Roomp and Rand 2009, Hebert and Bulliot 2010). For every cat, insulin efficiency was established based on the blood glucose curve interpretation, for which the following parameters were considered: a. initial blood glucose; b. onset time of insulin action; c. the nadir expressed in mg/dl (lowest point of glucose after insulin administration); d. duration of action - estimated from the administration, trough the nadir and to exceeding 270 mg/dl. Samples for blood glucose curve construction were prevailed prior to feeding and insulin administration at 0 hours, followed by every 60 to 120 minutes sampling, for 12 hours. Glycemic monitoring was instituted for all newly diagnosed cats or the ones undergoing dose adjustments and/or changing of insulin type. Data from the monitoring of blood glucose were graphically represented and interpreted to adapt the type and dose of insulin. When it was not possible to perform blood glucose monitoring, insulin dose never exceeded 1UI/cat/administration/day, preventing this way a possibly fatal hypoglycemia event (Rucinsky, Cook et al. 2010).

RESULTS AND DISCUSSIONS

The subclinical form of DM was identified in 6 (9.2%) patients diagnosed in an early-stage of the disease. Individuals in this group were identified either as a result of routine controls or evaluations for other purposes. Cats were presented in a stable general condition with very discrete characteristic DM clinical manifestations such as slightly increased appetite and discrete PU/PD syndrome, all considered signs of good health by owners. A number of 12 cats (18.4%) were presented with noticeable clinical DM manifestations: marked PU/PD, increased appetite with progressive weight loss and frequent vomiting episodes. Some cases also presented mild metabolic acidosis and liver steatosis, but kept a well preserved appetite. The remaining 47 cats were not eligible for inclusion in the study as they presented advanced forms of DM, with anorexia, severe metabolic acidosis and hepatic lipidosis. All cats with the complicated form of DM were submitted to an intensive treatment protocol, with soluble insulin until clinically stable. Glycemic curve was the main tool to determine insulin onset of action, the duration of effect, its effectiveness in reducing blood glucose level and most important detecting overdosing and preventing hypoglycaemia episodes (Jacquie Rand 2004). Ideal insulin effect exerted a nadir at 6 to 8 hours after administration, was maintained within 80-180 mg/dl and below renal threshold (<270 mg/dl) until next administration. A post-insulin blood glucose lower than 60-70 mg/dl, was observed in cats eating a smaller amount of food, or in cases of insulin overlap and potentiating effect of the two doses administered in one day. A nadir of 60 - 70 mg/dl, although within the reference range for feline blood glucose, holds an increased risk for the onset of hypoglycaemia, due to further activity of insulin (Bergman and Ader 2000, Hoenig, Thomaseth et al. 2007, Reusch 2011). Persistent hyperglycemia and glucose levels above 170 mg/dl were associated to insulin resistance, insulin underdosing, overeating and caloric excess when owners failed to comply with the prescribed diet and incorrect handling and administration of insulin by the owner. Mishandling and/or vigorous shaking of insulin vials can lead to insulin inactivation and loss hypoglycemiant effect (Lehninger 1982) due to the breaking of disulfide bonds joining the two terminals chains of insulin molecule.

Supplementary care was undertaken in cats suspected to present stress hyperglycemia. These cases were admitted to the clinic for at least three days, than were reevaluated. Removal of cats from the usual environment, especially of those that rarely leave their normal habitat and examination in a noisy environment, are all factors with a direct contribution to stress and registration of higher blood glucose values than the real ones. Stress hyperglycemia is explained as an adaptive response of the body under extreme conditions and is based on a surge of adrenaline, sympathetic nervous system stimulation and increases of catabolic hormones (Tappy 2008). Of these, glucagon and epinephrine lead to dissolution of glycogen stores, increasing blood glucose and reducing insulin mediated processes. Thus, stress or "fight or flight" reaction require a greater amount of energy substrate for central nervous system and skeletal muscles at the expense of parenchymal organs (Tappy 2008, Van Cromphaut 2009). An important consequence of stress hyperglycemia lies in the misinterpretation of blood glucose curve, consecutive insulin overdose and increased risk of hypoglycemic episodes.

In 15 cats, ideal control was obtained with insulin glargine, with a median dose 0.6 IU/kg (range: 0.2-1.1 IU/kg) administered twice daily. Insulin glargine hypoglycemiant effect always reached the second administration during the day. One case presented an overlapping effect of insulin doses administered in one day and further treatment was administrated once daily. A number of 11 cases (73.5% of the glargine treated group) treated with glargine insulin, were heading for remission and required a lower dose and in 9 cases only once daily administration. One case with concurrent stage IV kidney disease presented chronic Somogyi effect. This can be defined as a counter-regulatory effect, induced by insulin overdose, an abrupt drop in blood glucose level, followed by a rapid increase in blood glucose level in order to overcome life threatening hypoglycaemia. In this case, the insulin dose was reduced to 50% and the type of preparation was also changed from the synthetic long acting form, to the human premixed. The cat still presented strong fluctuations of insulin requirements and could not be equilibrated properly on the premixed insulin either. However the protocol managed to stop the chronic Somogyi effect.

Only 3 cases were managed with premixed isophane twice daily, with a median dose of 0.8 IU/kg (range: 0.4-1.9IU/kg). Two cases were treated with the premixed preparation due to insulin resistance induced by hypersomatotropism. The premixed insulin never exceeded a period of action of 8 hours and allowed reinstallation of hyperglycemia on a time interval varying from 2 to 4 hours before the next administration. Always, when transitioning from the fast-acting insulin to the intermediate and slow acting insulin, the dosing was reduced to 50% and adjusted further based on the blood glucose curve.

Generally, insulin treatment required twice daily administration for both types of insulin (Ettinger and Feldman 2005). Blood glucose level of clinically stable cats included in the study, was achieved in the majority of cats with long acting glargine insulin and in a reduced number with premixed insulin (Caney 2013). Insulin glargine, as in other studies (Mooney and Peterson 2012, Bloom and Rand 2014), had proven a beneficial superior effect, entailing a significantly lower incidence of hypoglycaemia (Roomp and Rand 2009, Roomp and Rand 2013). Only two cases treated with insulin glargine had sporadic subclinical episodes of hypoglycemia. The blood glucose of cats was kept under renal threshold throughout the day and from morning to evening dose. The rate of remission of cast treated

with glargine was 73.5%. Some studies have reported a contribution of insulin glargine to diabetes remission in up to 90% of cases, after a median of six months after starting treatment. Insulin glargine use in the specific therapy of feline type II DM is increasing gradually, with very good results (Maggiore 2015). Once injected into the subcutaneous compartment, the insulin forms a micro-precipitate and slowly release insulin, without having a strong peak of activity (Mooney and Peterson 2004). Although in humans the time of action can be up to 26 hours, fast metabolism of cats reduces the activity time to a median of 12h. Thus, in most cases, twice daily administration is necessary to adequately control blood glucose. As also seen in the current study, the slow onset of action of insulin glargine and absence of a pronounced peak, is associated with a significantly lower incidence of episodes of hypoglycaemia. The disadvantage of long acting insulin is overlap effect observed in some cases and a sudden stop in its action which might impose difficulties in establishing the appropriate dose. Also, insulin glargine can been associated with chronic Somogyi effect, as observed in one case in this study. Premixed insulin proved adequate only for three cases in the current study. It provided a better control than glargine in the insulin resistant acromegalic cats and in the cat with stage IV chronic kidney disease. In these cases insulin glargine failed to lower blood glucose under the renal threshold and only mild control was achieved with the premixed insulin. The advantage of premixed insulin analogues is the achieving of a fast hypoglycemiant effect, necessary at the time of food intake. Thus, this type of insulin gives an immediate insulin impulse after food ingestion, preventing postprandial hyperglycemia. Premixed insulin provides a very tight glycemic control, bringing blood glucose level within normal parameters, or under limits. However, most studies recommend keeping blood glucose under the renal barrier, as bringing blood glucose at the lower level or under normal parameters, can be associated with an extremely high risk of severe hypoglycemia, especially in cats with a varying appetite (Jacquie Rand 2004). Also, studies regarding insulin treatment in cats generally do not advice isophane insulin, unless no other type is available or proven to work (Mooney and Peterson 2012, Maggiore 2015).

CONCLUSION

Both premixed and long-acting insulins were administered only to clinically stable cats or as called “healthy” diabetics, which did not require intensive care therapy. Insulin glargine had a better effect in lowering blood glucose under the renal threshold and had the ability to keep hyperglycemia episodes under control between doses. Glargine insulin slow onset of action and absence of a pronounced peak were associated with a significantly lower incidence of hypoglycaemia episodes. The high rate of remission observed in cats treated with glargine is also in the favor of this type of insulin as first choice treatment agent. Premixed insulin provided a tight control bringing blood glucose to the lower normal range, but was highly associated with hypoglycemia episodes. Also, due to the accelerated metabolism of cats, isophane insulin activity did not reach the second administration in the day, thus cats were hyperglycemic for a varying length of time during the day.

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