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USE OF LISPRO INSULIN FOR TREATMENT OF DIABETIC KETOACIDOSIS IN CATS

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Abstract

Objectives: The aim of this study was to evaluate the efficacy and safety of lispro insulin for the treatment of feline diabetic ketoacidosis (DKA). Times to resolution of hyperglycemia, ketosis and acidosis were compared between cats treated with continuous rate infusion (CRI) of lispro insulin and cats treated with CRI of regular insulin.

Methods: Client-owned cats with naturally occurring DKA, newly diagnosed with diabetes mellitus (DM) or already on treatment for DM, were included. The diagnosis of DKA involved the presence of at least two clinical signs consistent with DKA (e.g., polyuria/polydipsia, anorexia, severe lethargy, vomiting and dehydration), blood glucose concentration > 13.9 mmol/L (> 250 mg/dL), blood beta hydroxybutyrate (BHB) concentration > 2.5 mmol/L and venous pH < 7.3 or bicarbonate < 15 mEq/L.

Cats were treated with a standard protocol with IV CRI of regular insulin (Group R) or lispro insulin (Group L). The time to resolution of DKA was defined as the time interval from when the IV CRI of insulin began until marked hyperglycemia (BG > 13.9 mmol/L [ > 250 mg/dL]), ketosis (BHB concentration > 1 mmol/L) and acidosis (venous pH < 7.3 and/or bicarbonate < 15 mEq/L) resolved.

Results: Eighteen DKA cases (nine per group) were enrolled into the study. There were no significant differences in the median time to resolution of three variables (hyperglycemia, ketosis and acidosis) between the two groups. Two cats in Group R developed hypoglycaemia during the CRI of insulin. One cat in Group L and three cats in Group R developed hypophosphataemia, which required phosphate supplementation.

Conclusions and relevance: Intravenous CRI of insulin lispro has few side effects and appears to be as effective as IV CRI regular insulin in the treatment of cats with DKA.
Diabetic ketoacidosis (DKA) is the most common complication of naturally occurring diabetes mellitus (DM) and is characterized by a biochemical triad of hyperglycaemia, ketosis and acidosis. Treatment of DKA comprises intravenous (IV) fluid resuscitation, correction of acid/base and electrolyte derangements, insulin therapy and targeted therapy for comorbid conditions.

During DKA regular insulin is usually administered intramuscularly or intravenously in cats and dogs; in humans it is also injected subcutaneously. Nevertheless, the dehydration and shock state of patients with DKA leads to erratic and inconstant absorption of intramuscular and subcutaneous insulin. For this reason, IV infusion of regular insulin has been the mainstay of treatment of DKA as it causes a more predictable fall in blood glucose and it allows for rapid adjustments.

Insulin lispro is a genetically engineered analogue of human insulin in which proline at position B28 and lysine at position B29 are inverted in their sequence reducing the formation of insulin dimers and hexamers. This structural change ensures more rapid absorption and elimination from the subcutaneous injection site, resulting in the rapid onset and a short duration of hypoglycaemic activity. Furthermore, one study in human medicine comparing the end-organ metabolic effects of intravenous lispro insulin, regular insulin and glulisine insulin showed that all these insulins have similar effects on the suppression of endogenous glucose production, glucose uptake and free fatty acid, glycerol and lactate levels. The success of lispro insulin, as well as other insulin analogues, has gradually reduced the use of regular insulin, as demonstrated by Eli Lilly’s financial report. Assuming that the production of regular insulin may be discontinued, a valid alternative for treating DKA in dogs and cats should be found. Two studies demonstrated that IV continuous rate infusion (CRI) of lispro and aspart insulin is safe and appears to be as effective as IV CRI regular insulin for the treatment of canine DKA.

The aim of this study was to evaluate the efficacy and safety of lispro insulin for the treatment of feline DKA by comparing the times to resolution of hyperglycaemia, ketosis and acidosis between cats treated with CRI of lispro insulin and cats treated with CRI of regular insulin.

Materials and methods
Client-owned cats admitted to the University Veterinary Hospital of Bologna (Italy) between May 2009 and March 2017 with naturally occurring DKA, either newly diagnosed with DM or with known DM, were considered for inclusion. The diagnosis of DKA involved the presence of at least two clinical signs consistent with DKA (e.g., polyuria/polydipsia, anorexia, severe lethargy, vomiting and dehydration), blood glucose concentration > 13.9 mmol/L (> 250 mg/dl), blood beta hydroxybutyrate (BHB) concentration > 2.5 mmol/L and venous pH < 7.3 or bicarbonate < 15 mEq/L. Cats with DKA, admitted between May 2009 and February 2012, and treated with a protocol for insulin therapy adapted from a published protocol using IV CRI of regular insulin (Humulin R, Ely Lilly and Co, Indianapolis, IN) were used as part of the control group of this study.

From March 2012 to April 2014 cats with DKA admitted to the University Veterinary Hospital were treated with the same insulin protocol but using lispro insulin (Humalog, Eli Lilly and Co), until the number of cats was the same in both groups. Between May 2014 and March 2017, cats admitted for DKA were alternately treated with regular insulin or lispro insulin. Cases were divided according to whether they received IV CRI of regular insulin (Group R) or IV CRI of lispro insulin (Group L). Cats with multiple hospitalizations for DKA management during the study period were included in the analyses with each hospitalization event treated as a separate case.

Cases were excluded from the study if they had unavailable or missing medical records and if they died or were euthanized prior to administration of insulin therapy. The trial was approved by the Scientific Ethics Committee, University of Bologna, Italy. Owners signed the written informed consent before enrollment in the study.

At the time of admission to the hospital, history, physical examination findings and results of blood gas analysis, complete blood count (CBC), serum biochemistry profile, urinalysis and bacterial culture from urine collected via cystocentesis were performed in each cat in order to confirm DKA and identify any concurrent disorder. An abdominal ultrasound was performed in order to detect any abnormalities (e.g., acute pancreatitis, neoplasia). Thoracic radiographs or other diagnostic tests were also performed according to the clinician’s discretion.

Definitions of “resolution time” of hyperglycaemia, ketosis, acidosis and ketoacidosis, and of the time of subcutaneous insulin administration and length of hospitalization
The “resolution time” for the variables hyperglycaemia, ketosis and acidosis was calculated starting from “time zero”, which was the time at which IV CRI of insulin treatment was initiated. The time to resolution of pronounced hyperglycaemia was defined as the time interval between “time zero” and the time at which the blood glucose concentration fell to < 13.9 mmol/L (< 250 mg/dl). The time to resolution of ketosis was defined as the time interval between “time zero” until BHB was \( \leq 1.0 \) mmol/L for two consecutive measurements 1 hour apart. The time to resolution of acidosis was defined as the interval between “time zero” and the time at which venous pH was \( \geq 7.3 \) and/or bicarbonate \( \geq 15 \) mEq/L. The time to resolution of ketoacidosis was defined as the time interval between “time zero” and the time at which ketosis and acidosis had both resolved. The IV CRI of insulin was stopped when ketosis and acidosis had resolved and the cat was eating well.

The time to subcutaneous (SC) insulin administration was defined as the time interval from the resolution of ketoacidosis (when the transition from the intravenous to the subcutaneous insulin administration occurs) up to the hospital discharge. The length of hospitalization (LOH) was defined as the time interval between “time zero” and discharged from the hospital.

**Monitoring protocol**

Blood glucose was monitored hourly during the first 24 hours with a hand-held glucometer, previously validated for cats (Optium Xceed, Optium Glucose Test Strips; Abbott Laboratories), and then every 2-3 hours during the entire time that the cat received an IV CRI of insulin. Blood BHB was measured every 4 hours using a portable ketometer, previously validated for cats (Optium Xceed, Optium β-ketone Test Strips; Abbott Laboratories) until BHB was \( \leq 1.0 \) mmol/L; in this case the BHB was measured 1 hour later and if a BHB \( \leq 1.0 \) mmol/L was confirmed then ketosis was deemed to be resolved. A blood gas analysis (including pH, base excess, serum bicarbonate, sodium, potassium, ionized calcium and lactate) was performed with a point-of-care analyser (Idexx VetStat, Idexx Laboratories, Italy) every 8 hours during the first 24 hours, and then every 12 hours until ketosis was resolved.
Insulin-induced hypoglycaemia was defined as a blood glucose concentration < 4.4 mmol/L (< 80 mg/dL); hypokalaemia was defined as serum potassium < 3.6 mEq/L. Hypophosphataemia was defined as serum phosphate < 0.5 mmol/L (< 1.5 mg/dL).

Treatment protocol

Upon admission, all cats were treated with intravenous crystalloids (Ringer Lactate or Acetate or 0.9% NaCl) prior to and while receiving insulin treatment. The initial rate of fluid administration was determined by the attending clinician to meet the specific rehydration needs of each cat. Intravenous insulin CRI was initiated from 2 to 8 hours after fluid administration had been started, depending on clinician’s perception that severe dehydration had resolved. The insulin solution, which was administered in a separate line from the fluids, consisted of 48 mL of 0.9% NaCl to which 1.1 units per kg body weight of lispro insulin or regular insulin were added. To saturate binding of insulin to the IV tubing, the insulin solution was allowed to stand in the line for 30 min and then run through the IV line. At this point, the insulin solution was re-prepared and the infusion was started. The initial insulin CRI rate was based on the patient’s blood glucose concentration when the CRI was started (“time zero”) (Table 1). The rate of insulin CRI was adjusted every 1-2 hours based on the patient’s blood glucose. Adjustments to the insulin CRI rate and the addition of dextrose were implemented at each clinician’s discretion based on previously published guidelines (Table 1). Long-term insulin was initiated when ketoacidosis was resolved and the cat was eating and appropriately hydrated.

Serum potassium concentration was corrected as previously described. If serum phosphate concentration decreased to < 0.5 mmol/L (< 1.5 mg/dL) it was corrected by administration of IV CRI of potassium phosphate at a rate of 0.01-0.03 mmol phosphate/kg/h for 6 hours and then phosphatemia was re-evaluated. Supplementation with potassium was taken into account when giving potassium phosphate for correction of hypophosphataemia. Antimicrobials were administered to all cats for the duration of hospitalization; additional drugs including gastroprotectants, antiemetics and analgesics were administered as deemed appropriate by the attending clinician according to the clinical condition and concurrent disorders.
Statistical methods

Statistical analysis was performed using commercially available software (GraphPad Prism 5, GraphPad Software Inc., San Diego, CA). Due to the small number of cases in each group, continuous variables were considered to be nonparametric and descriptive statistics are reported as median (minimum, maximum). The Mann Whitney U-test was used to compare variables between the two insulin groups. The Wilcoxon signed rank test was used to compare changes from baseline of the continuous variables within each insulin group. A P-value < 0.05 was considered significant. In order to compare the different variables between cats with newly diagnosed DM and cats with known DM, regardless of the type of insulin used, Mann Whitney U-test was used.

Results

Twenty-four diabetic ketoacidosis cases were evaluated in the study period. Four cases were excluded because cats died or were euthanized before initiating insulin CRI therapy, and two cases were excluded because of incomplete medical records. A total of 18 cases in 15 cats were included in the study; one cat had three DKA events (in two events received lispro insulin and in another one received regular insulin) and another cat had two DKA events during the study period (in one received lispro insulin and in the other received regular insulin). Nine cases were managed with lispro insulin (Group L) and nine cases were managed with regular insulin (Group R). In fifteen cases cats were discharged from the hospital; one cat from Group L died and two cats from Group R were euthanized; these three cats were newly diagnosed with DM.

Symptoms, history, clinical signs and physical examination findings

There was no significant difference between groups with regards to the median age, body weight, breed and sexual status (neutered or intact) (Table 2). The median age among all 18 cases was 10.4 years (range, 7.7-16.5 years). The median body weight of all 18 cases was 4.5 kg (range, 2.6-8 kg) and their median body condition score (BCS) was 6.5 (range, 2-8). All fifteen cats included in the study were European short hair cats except one Persian cat in group R and one Birman cat in group L. Eight cats were neutered males, five were neutered females, one was an intact male and one was an intact female.
In 10 cases cats were newly diagnosed with DM at the time of enrollment into the study. In 8 cases (7 cats), cats had previously been diagnosed with DM (five in Group L and three in Group R), a median of 8 months (range, 1-12 months) prior to enrollment into the study, and they were all receiving glargine insulin (Lantus, 100 U/mL glargine, Aventis Pharmaceuticals, Germany). Insulin dosage at the time of enrollment into the study was 0.5 U twice daily in one cat, 1 U twice daily in four cats, 2 U twice daily in two cats and 2.5 U twice daily in one cat.

Clinical signs observed by the owner prior to admission into the hospital included lethargy (observed in 15 of 18, 83%), anorexia (15 of 18, 83%), polyuria and polydipsia (10 of 18, 56%), vomiting (6 of 18, 33%), weight loss (5 of 18, 28%), asthenia (4 of 18, 22%) and diarrhoea (3 of 18, 17%). Medications administered to the cats at the time of admission into the hospital included insulin (7 of 18), tylosin (2 of 18), methimazole (Tapazole®) (1 of 18), marbofloxacin (Aristos®) (1 of 18) and enrofloxacin (Baytril®) (1 of 18).

At the time of admission, the most common abnormalities included some degree of dehydration (observed in 17 of 18, 94%), dull or depressed mentation (17 of 18, 94%), hypothermia (8 of 18, 44%), overweight body condition (7 of 18, 39%), underweight body condition (5 of 18, 28%), pale mucous membranes (5 of 18, 28%), jaundice (4 of 18, 22%), muscle atrophy (3 of 18, 17%), heart murmur (2 of 18, 11%) and palpable thyroid nodule (1 of 18, 6%).

**Clinicopathological findings**

At the time of admission into the hospital, median blood glucose concentration, BHB concentration, venous pH and serum bicarbonate concentration did not differ significantly between the lispro insulin and regular insulin-treated group (Table 2).

The median blood glucose concentration in Group L and Group R was 20.8 mmol/L (range, 12.4-35 mmol/L) (374 mg/dL [224-630 mg/dL]) and 22.9 mmol/L (12.4-41.3 mmol/L) (413 mg/dL [224-744 mg/dL]), respectively. At “time zero”, the median blood glucose concentration was 22.5 mmol/L (11-27.8 mmol/L) (405 mg/dL [198-500 mg/dL]) and 21.7 mmol/L (13.4-27.8 mmol/L) (391 mg/dL [241-500 mg/dL]) in Group L and Group R, respectively. No significant differences were detected in blood glucose concentration between the two
treatment groups at the time of admission ($P = 0.69$) or at “time zero” ($P = 0.86$). The rate of decrease in blood glucose concentration was $< 5.6$ mmol/L/h (100 mg/dl/h) in all 18 cases during the entire study.

The median BHB concentration in Group L and Group R was 6.2 mmol/L (range, 3.7-8 mmol/L) and 7.2 mmol/L (4.9-8 mmol/L), respectively. At “time zero”, the median BHB concentration was 5.4 mmol/L (4.2-7.8 mmol/L) and 7.2 mmol/L (4.7-8 mmol/L) in Group L and Group R respectively. No significant differences were detected in BHB concentration between the two treatment groups at the time of admission ($P = 0.42$) or at “time zero” ($P = 0.13$).

At the time of admission, there were also no significant differences between the two treatment groups with respect to any of the biochemical parameters analysed (Table 2).

The median time interval between the time at which fluid therapy was initiated until “time zero” was 4 hours in the lispro insulin group (range, 2-8 h) and 4.5 hours (range, 1-8 h) in the regular insulin group; there was no significant difference between the two groups ($P = 0.62$).

**Adverse drug reactions**

No local or systemic adverse effects associated with IV insulin administration were noted in either group. Two cats in Group R developed hypoglycaemia during the CRI of insulin (4.39 mmol/L [79 mg/dL] and 2.22 mol/L [40 m g/dL] respectively), but these cats did not show clinical signs compatible with hypoglycaemia. In all 18 cases, cats developed transient hypokalaemia during the study. Median minimum potassium concentrations did not differ significantly between the lispro (2.8 mmol/L; range 2.2-3.7 mmol/L) and regular (2.6 mmol/L; range 2.2-3.5 mmol/L) insulin treatment groups ($P = 0.82$). One cat in Group L and three cats in Group R developed hypophosphataemia which required supplementation during the study.

**Resolution time of hyperglycaemia, acidosis and ketosis, time of SC insulin administration and LOH**

Severe hyperglycemia resolved in all 18 cases, acidosis resolved in 15 cases (7 in Group L and 8 in Group R) and ketosis resolved in 16 cases (8 in Group L and 8 in Group R). One cat in Group L died prior to resolution of acidosis and ketosis. Acidosis did not resolve in one cat in Group L and one cat in Group R that had suffered an
acute kidney injury (AKI) at the time of admission; ketosis did not resolve in one other cat in Group R, possibly
due to the insulin-resistance secondary to a concurrent carcinoma.

There were no significant differences in the median time to resolution of three variables (hyperglycaemia,
ketosis and acidosis) between the two groups when evaluated separately; there was no significant difference in
the median time to resolution of ketoacidosis (Table 3).

The median times to resolution of severe hyperglycaemia in Group L and Group R were 8 hours (range, 0-25 h)
and 9 hours (range, 0-24 h), respectively ($P = 0.72$). The median time to resolution of ketosis was 29 hours
(range, 16-94 h) in Group L and 26.5 hours (range, 21-53 h) in Group R ($P = 0.83$). The median time to
resolution of acidosis in Group L and Group R was 8 hours (range, 8-32 h) and 20 hours (range, 8-48 h),
respectively ($P = 0.26$). The median time to resolution of ketoacidosis in Group L and Group R was 33 hours
(range, 16-94 h) and 28 hours (range, 21-53 h), respectively ($P = 1$).

There were no significant differences between newly diagnosed and previously diagnosed diabetic cats with
respect to median time to resolution of hyperglycaemia and ketosis (analysed separately), and ketoacidosis
(Table 4). However, the median time to resolution of acidosis in the newly diagnosed diabetics (12 h; range, 8-
24 h) was significantly shorter than in previously diagnosed diabetics (24 h; range, 8-48 h; $P = 0.02$).

Venous pH decreased during the first hours of treatment, before it began to rise, in five of 18 cases, (one case in
Group L and four cases in Group R). The lowest pH for these five cases was reached at a median of 8 hours
(range, 8-16 h) from the time at which fluid infusion had begun. The median lowest pH for the five cases in
which this initial decline occurred was 7.07 (range, 6.94-7.25), and did not differ significantly ($P = 0.06$) from
the pH of the same patients at admission (median 7.15; range 7.02-7.28). Also there was no significant
difference in length of hospitalization between cases in which pH decreased before it began to rise and cases in
which this did not happen.

The median time to administration of SC insulin, in the 15 cases that were discharged, did not differ significantly
between Group L (76 h; range, 34-168 h) and Group R (89 h; range, 48-244 h; $P = 0.25$). Likewise the median
duration of hospitalization for these 15 cases, did not differ significantly between Group L (110.5 h; range, 74-
268 h) and Group R (146 h; range, 94-294 h; $P = 0.18$) (Table 3).
No significant differences were found in median time to administration of SC insulin and in median duration of hospitalization between newly diagnosed and previously diagnosed diabetic cats (Table 4).

The lispro insulin-treated cat that died had been hospitalized for 45 hours at the time of death; the two cats treated with regular insulin that were euthanized had been hospitalized for 106 and 129 hours respectively at the time of euthanasia.

**Evaluation for presence of concurrent disorders**

Based on the diagnostic protocol, concurrent disorders were identified in 11 cases (five in Group L and six in Group R). In Group L, two cases had inflammatory bowel disease, one cat had pancreatitis, one cat had concurrent pancreatitis, lipidosis and acute kidney injury and one cat had pulmonary neoplasia. In Group R, one cat was diagnosed with a bacterial urinary tract infection based on urinary culture, one cat was diagnosed with pancreatitis and inflammatory bowel disease, one cat had pancreatitis and polycystic kidney disease, one cat had hyperthyroidism and herpesvirus infection, one cat had chronic kidney disease and one cat had a giant cell tumor.

The diagnosis of pancreatitis was based on abdominal ultrasound (enlarged, irregular, hypoechoic pancreas surrounded by hyperechoic mesentery, and mild-to-moderate ascites) and positivity to a feline pancreatic lipase immunoreactivity (fPLI) test.

**Discussion**

Lispro insulin was developed to resolve the problems associated with the use of regular human insulin (peak of activity reached too late, hypoglycaemic effect possibly lasting too long) by subcutaneous injection. The major difference between lispro insulin and regular insulin is the rate of their self-disassociation, which causes differences in the rate of absorption from the injection site. However this difference may not exist with intravenous administration. A study on rabbits showed that the hypoglycaemic response profiles after intravenous administration of lispro insulin and regular human insulin were very similar in pattern and confirmed that their biological activities are equivalent.
The aim of this study was to evaluate the efficacy and safety of lispro insulin for the treatment of feline DKA.

The need to test a new insulin, which could provide an alternative to regular insulin, has arisen because insulin analogues are widely used for the management of DM and treatment of uncomplicated DKA in human medicine, although some patients with severe comorbidities still require intensive care and IV insulin administration.\textsuperscript{8,21-24}

It is possible that the production of regular insulin may be discontinued in the future, and since only regular insulin is currently indicated for the treatment of DKA with the constant low-dose intravenous insulin infusion technique in cats, a viable alternative to regular insulin will need to be found to manage these patients.

In a prospective randomized study, Sears et al. compared the efficacy and safety of IV CRI of lispro with that of regular insulin in a population of 12 dogs with DKA.\textsuperscript{13} They observed comparable improvement in glycaemia, ketosis and acidosis between the two groups and the time to resolution of ketoacidosis was significantly shorter in the lispro insulin group, though the length of hospitalization did not differ significantly. They concluded that IV CRI of lispro insulin is safe and appears to be as effective as IV CRI of regular insulin for the treatment of canine DKA.

In our study on feline DKA, the time of resolution of hyperglycaemia, ketosis, acidosis and ketoacidosis was similar in cases treated with lispro insulin and those treated with regular insulin; also the time of SC insulin administration and the LOH did not differ significantly between the two groups. Nevertheless the time to resolution of acidosis and the LOH were both shorter in the group of cases treated with lispro insulin, although these differences were not significant. A number of variables, including concurrent disorders, may have contributed to these findings, and it seems reasonable to suppose that studying a larger group of cases in the future could reveal that each of these times is significantly shorter with lispro insulin treatment.

The median time to resolution of acidosis in the newly diagnosed diabetic cats was significantly shorter than in previously diagnosed diabetics; this result may reflect a different efficiency in the buffering system and a difference in acid-base status between newly and previously diagnosed diabetic cats.

In the first hours after the onset of insulin therapy, venous pH decreased before it began to rise in only one cat in Group L and in four cats in Group R; these results could be attributed to the more rapid action of lispro insulin compared to regular insulin. Furthermore, hyperglycaemia resolved in all 18 cases, acidosis resolved in 7/9 cases
in Group L and in 8/9 cases in Group L, and ketosis resolved in 8/9 cases in Group L and Group R. On the basis of these results IV CRI of lispro insulin appears to be as effective as IV CRI of regular insulin for the treatment of cats with DKA.

With regards the safety, on our results, side effects were seen less frequently in cases treated with lispro insulin than in cases treated with regular insulin; in fact, in Group R in 2 occasions cats developed hypoglycaemia and in 3 developed hypophosphataemia; while only one cat in Group L developed hypophosphataemia. Despite supplementation, transient hypokalaemia occurred in all cats during the IV infusion of insulin, regardless of the type of insulin. Although hypokalaemia that develops during DKA rarely becomes symptomatic, in our opinion it would be more appropriate to use higher rates of supplementation than those normally reported in textbooks during the first hours of insulin therapy; this was also suggested by Nelson, but only in those patients with normal urinary production and if frequent assessments of kalaemia are possible.²

In this study there were no significant differences in blood glucose concentration or BHB concentration between the two treatment groups at the time of admission or at “time zero”, when insulin therapy began. On the contrary, a decrease in blood glucose concentration during the first hours of fluid therapy has been reported in human medicine and in some studies in veterinary medicine, and has been attributed to rehydration-induced renal excretion of glucose, decreased concentrations of the counterregulatory hormones or improved perfusion and delivery of endogenous insulin.¹³⁻¹⁴,²⁵⁻²⁶ This reduction was not observed during our study, probably due to the conservative fluid therapy, which was not too “aggressive”. On that note, one of the current study’s limitations is the lack of standardized criteria for the evaluation of the degree of dehydration (determined subjectively) to determine when to start insulin therapy.

Another important limitation is the small number of cases enrolled which influenced the power of statistics. It is likely that some differences between groups were not detected because of this bias. Furthermore, some cats were included more than once and this is also a possible bias; in fact it is possible that a cat responds in a similar manner with repeated treatment compared with a different cat, or that a cat can be more severely affected with subsequent visits because of progression of concurrent illness or even less severely affected because owners recognized the signs earlier.
Finally, other study’s limitations are the absence of randomization and the heterogeneity of the population with regard to the presence of concurrent disorders. However, our population’s characteristics were very similar to those in other studies about feline DKA suggesting that this small population is representative of cats with spontaneous DKA.

In conclusion, the results demonstrate that IV CRI lispro insulin treatment did not show severe side effects in cats of this study and appears to be as effective as IV CRI regular insulin treatment in managing cats with DKA.

References


Table 1: Sliding scale for adjustment of IV CRI insulin treatment and dextrose supplementation for cats with diabetic ketoacidosis.

<table>
<thead>
<tr>
<th>Blood glucose concentration (mmol/L) (mg/dL)</th>
<th>Fluids</th>
<th>Rate of administration of insulin solution (mL/h)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;13.9 (&gt;250)</td>
<td>0.9% NaCl or Ringer</td>
<td>2</td>
</tr>
<tr>
<td>11.1–13.9 (200-250)</td>
<td>2.5% dextrose*</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Group L</td>
<td>Group R</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.5 (8.25-14.2)</td>
<td>10.25 (7.75-16.5)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>4.8 (2.8-5.7)</td>
<td>4.2 (2.6-8)</td>
</tr>
<tr>
<td>Male : female</td>
<td>4 : 5</td>
<td>5 : 4</td>
</tr>
<tr>
<td>Spayed</td>
<td>5/9</td>
<td>3/9</td>
</tr>
<tr>
<td>Castrated</td>
<td>4/9</td>
<td>4/9</td>
</tr>
<tr>
<td>Female</td>
<td>0/9</td>
<td>1/9</td>
</tr>
<tr>
<td>Male</td>
<td>0/9</td>
<td>1/9</td>
</tr>
<tr>
<td>Blood glucose concentration (mmol/l) [RR 4.1-8.8 mmol/l]</td>
<td>20.8 (12.4-35)</td>
<td>22.9 (12.4-41.3)</td>
</tr>
<tr>
<td>Blood glucose concentration (mmol/l) at &quot;time zero&quot; [RR 4.1-8.8 mmol/l]</td>
<td>22.5 (11-27.8)</td>
<td>21.7 (13.4-27.8)</td>
</tr>
<tr>
<td>BHB concentration (mmol/l) [RR &lt; 2.5 mmol/l]</td>
<td>6.2 (3.7-8)</td>
<td>7.2 (4.9-8)</td>
</tr>
<tr>
<td>BHB concentration (mmol/l) at &quot;time zero&quot; [RR &lt; 2.5 mmol/l]</td>
<td>5.4 (4.2-7.8)</td>
<td>7.2 (4.7-8)</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/l) [RR 18-23.2 mmol/l]</td>
<td>12.9 (8.2-30.2)</td>
<td>12.1 (7.8-17.6)</td>
</tr>
<tr>
<td>Venous pH [RR &lt; 7.3]</td>
<td>7.16 (7.02-7.24)</td>
<td>7.15 (7.06-7.28)</td>
</tr>
<tr>
<td>CO₂ (mmol/l) [RR 29.8 (25.2-40.6)]</td>
<td>37.6 (22.6-43.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Sodium (mmol/l) [RR 141-155 mmol/l]</td>
<td>148 (131-154)</td>
<td>148 (135-165)</td>
</tr>
<tr>
<td>Potassium (mmol/l) [RR 3.6-5.8 mmol/l]</td>
<td>3.3 (2.2-4.4)</td>
<td>3.9 (2.5-4.6)</td>
</tr>
<tr>
<td>Chloride (mmol/l) [RR 119-132 mmol/l]</td>
<td>116 (92-122)</td>
<td>109 (83-126)</td>
</tr>
<tr>
<td>Creatinine (µmol/l) [RR 70.7-159.1 µmol/l]</td>
<td>119 (80-273)</td>
<td>156 (93-254)</td>
</tr>
<tr>
<td>Phosphate (mmol/l) [RR 1.04-2.69 mmol/l]</td>
<td>1.4 (1.2-1.8)</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Calcium (mmol/l) [RR 1.5-2.63 mmol/l]</td>
<td>2.38 (2-2.48)</td>
<td>2.38 (1.93-2.53)</td>
</tr>
<tr>
<td>Total protein (g/l) [RR 60-80 g/l]</td>
<td>74.4 (57.5-93.5)</td>
<td>77.1 (52.8-85.8)</td>
</tr>
<tr>
<td>Albumin (g/l) [RR 21-33 g/l]</td>
<td>32.2 (24.4-39.3)</td>
<td>31 (22.8-34.7)</td>
</tr>
<tr>
<td>AST (U/l) [RR 14-41 U/l]</td>
<td>154 (48-1849)</td>
<td>113 (18-291)</td>
</tr>
<tr>
<td>ALT (U/l) [RR 22-45 U/l]</td>
<td>216 (98-1478)</td>
<td>154 (34-237)</td>
</tr>
<tr>
<td>ALP (U/l) [RR 0-120 U/l]</td>
<td>76 (32-193)</td>
<td>40 (32-82)</td>
</tr>
<tr>
<td>GGT (U/l) [RR 0-3 U/l]</td>
<td>0.4 (0.1-1.2)</td>
<td>0.1 (0.1-2)</td>
</tr>
<tr>
<td>Total bilirubin (µmol/l) [RR 0.11-9.8 µmol/l]</td>
<td>4.4 (2.2-65.1)</td>
<td>9.6 (3.8-64.9)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l) [RR 1.65-5.94 mmol/l]</td>
<td>5.9 (3.3-8.0)</td>
<td>8.5 (1.8-11.1)</td>
</tr>
</tbody>
</table>

Data are expressed as median; values in parentheses indicate range. RR = reference range for healthy cats. Data were compared with Mann-Whitney U-tests.

| Table 2: Baseline data and blood glucose and BHB concentration at “time zero” in cats with diabetic ketoacidosis treated with IV CRI of lispro insulin (Group L) and treated with IV CRI of regular insulin (Group R). |

* Insulin solution composed of 1.1 U/kg of regular or lispro insulin added to 48 mL of 0.9% NaCl.

a 2.5% dextrose composed of 25 mL dextrose 50% added to 475 mL of 0.9% NaCl or Ringer.

b 5% dextrose composed of 50 mL dextrose 50% added to 450 mL of 0.9% NaCl or Ringer.
Table 3: Time to resolution of hyperglycaemia, ketosis, acidosis and ketoacidosis, time of subcutaneous insulin administration and length of hospitalization in cats with diabetic ketoacidosis treated with IV CRI of lispro insulin (Group L) and treated with IV CRI of regular insulin (Group R).

<table>
<thead>
<tr>
<th></th>
<th>Group L</th>
<th>Group R</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution time of hyperglycaemia (h)</td>
<td>8 (0-25)</td>
<td>9 (0-24)</td>
<td>0.72</td>
</tr>
<tr>
<td>Resolution time of ketosis (h)</td>
<td>29 (16-94)</td>
<td>26.5 (21-53)</td>
<td>0.83</td>
</tr>
<tr>
<td>Resolution time of acidosis (h)</td>
<td>8 (8-32)</td>
<td>20 (8-48)</td>
<td>0.26</td>
</tr>
<tr>
<td>Resolution time of ketoacidosis (h)</td>
<td>33 (16-94)</td>
<td>28 (21-53)</td>
<td>1</td>
</tr>
<tr>
<td>Time of SC insulin administration (h)</td>
<td>76 (34-168)</td>
<td>89 (48-244)</td>
<td>0.25</td>
</tr>
<tr>
<td>Length of hospitalization (h)</td>
<td>110.5 (74-268)</td>
<td>146 (94-294)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Data are expressed as median; values in parentheses indicate range.

Table 4: Time to resolution of hyperglycaemia, ketosis, acidosis and ketoacidosis, time of subcutaneous insulin administration and length of hospitalization in cats with diabetic ketoacidosis, comparing cats with newly diagnosed diabetes mellitus and cats with known diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>Newly diagnosed DM</th>
<th>Known DM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution time of hyperglycaemia (h)</td>
<td>9 (0-15)</td>
<td>10 (4-25)</td>
<td>0.37</td>
</tr>
<tr>
<td>Resolution time of ketosis (h)</td>
<td>25 (21-51)</td>
<td>40 (16-94)</td>
<td>0.96</td>
</tr>
<tr>
<td>Resolution time of acidosis (h)</td>
<td>12 (8-24)</td>
<td>24 (8-48)</td>
<td>0.02</td>
</tr>
<tr>
<td>Resolution time of ketoacidosis (h)</td>
<td>26.5 (21-51)</td>
<td>42 (16-94)</td>
<td>0.48</td>
</tr>
<tr>
<td>Time of SC insulin administration (h)</td>
<td>70.5 (34-244)</td>
<td>87 (48-177)</td>
<td>0.3</td>
</tr>
<tr>
<td>Length of hospitalization (h)</td>
<td>97 (74-292)</td>
<td>137 (81-294)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Data are expressed as median; values in parentheses indicate range.