Received: 9 July 2018 | Accepted: 3 May 2019

DOI: 10.1111/jvim.15518

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Lispro insulin and electrolyte supplementation for treatment of diabetic ketoacidosis in cats

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Funding information
Dr. Emily Friedman, Gift

Abstract

Background: Intravenous continuous rate infusion (IVCRI) of lispro at a starting dose of 0.09 U/kg/h and the use of 0.9% sodium chloride (NaCl) for fluid resuscitation in cats with diabetic ketoacidosis (DKA) have not been reported. Protocols for correction of electrolyte deficiencies in cats with DKA are lacking.

Objectives: To characterize the use of IVCRI lispro at an initial dose of 0.09 U/kg/h and the use of NaCl for resuscitation. Explore protocols for electrolyte supplementation in cats with DKA.

Animals: Twelve cats with DKA enrolled from the cat population of a university hospital.

Methods: Randomized, controlled, blinded study. Six cats were randomized into each group, the lispro insulin treatment group (LITG) and regular insulin treatment group (RITG). All cats received IVCRI fluid resuscitation with NaCl. Solutions with higher than previously published electrolyte concentrations were used to treat electrolyte deficiencies.

Results: The median time to blood glucose (BG) concentration <250 mg/dL was significantly shorter in the LITG (median 7 hours, 2-10 hours) than the RITG (median 12.5 hours, 8-20 hours; $P = .02$). Two cats had nonclinical hypoglycemia (BG = 40 mg/dL). The most rapid change in 157 measurements of corrected sodium concentrations was 0.7 mmol/L/h. Low concentrations of serum sodium, potassium, phosphate, and magnesium were over 3 times more common than above normal electrolyte concentrations, despite supplementation with fluids of high electrolyte concentrations.

Conclusions and Clinical Importance: Lispro at a starting dose of 0.09 U/kg/h and NaCl administered for fluid resuscitation are safe and effective for treatment of DKA in cats.

KEYWORDS
magnesium, phosphate, potassium, saline, sodium

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a severe, potentially life-threatening complication of diabetes mellitus (DM) in cats.[1] Protocols for treatment of

Abbreviations: BG, blood glucose; BOHB, beta-hydroxybutyrate; DKA, diabetic ketoacidosis; DM, diabetes mellitus; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; IVCRI, Intravenous continuous rate infusion; LITG, lispro insulin treatment group; NaCl, sodium chloride; PLI, pancreatic lipase immunoreactivity; RITG, regular insulin treatment group.

DKA in cats include the use of IV continuous rate infusion (IVCRI) regular insulin, intermittent IM injection of regular insulin, a combination of IM regular insulin and SC glargine, or a combination of IM and SC glargine.[1-4] The use of IVCRI lispro insulin for treatment of DKA in cats has also been described in a case series in which cats were treated with an initial insulin dose 0.045 U/kg/h. [5] It is important to validate alternative IVCRI insulin treatment protocols because the production of regular insulin could be discontinued. According to the 2017 annual report of Eli Lilly, the revenue associated with lispro is now more than double the revenue associated with regular insulin (https://investor.lilly.com/financial-information/annual-reports). Additionally, the patent for lispro has expired in several countries, and a Sanofi-Aventis lispro insulin has been granted FDA approval in the United States and European Medicines Agency approval in the European Union (https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm588466.htm; http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004303/human_med_002129.jsp&mid=WC0b01ac058001d124). These factors could contribute to a more competitive pricing of lispro and could influence its use in veterinary medicine.

Lispro is a genetically engineered human analogue insulin in which proline at position B28 and lysine at position B29 are transposed.[6] In humans with critical illness, IVCRI of lispro more rapidly decreases blood glucose (BG) concentration, and with lower risk of hypoglycemia, compared to IVCRI of regular insulin.[7] In dogs, the median time to resolution of hyperglycemia, ketosis, and acidosis with IVCRI of lispro is significantly shorter (26 hours; range 26-50 hours) than in dogs treated with IVCRI of regular insulin (61 hours; range, 38-80 hours; $P = .02$) when the initial insulin dose of both products is 0.09 U/kg/h.[8] In cats, the median times to resolution of hyperglycemia, ketosis, or acidosis with IVCRI of lispro are not significantly different (8, 29, or 8 hours, respectively) than these times when cats are treated with IVCRI of regular insulin (9, 26.5, or 20 hours, respectively) when the initial insulin dose of both products is 0.045 U/kg/h.[5] The median times to resolution of hyperglycemia, ketosis, or acidosis in cats with intermittent IM regular insulin administered in combination with SC glargine insulin are significantly shorter (9, 44, or 23 hours, respectively) than times in cats treated with IVCRI of regular insulin (12, 62, or 41 hours, respectively) when the initial insulin dose of the IVCRI is 0.045 U/kg/h.[3] For the purpose of the current study, an initial IVCRI insulin dose of 0.09 U/kg/h (prepared by adding 2.2 U/kg/240 mL bag of 0.9% NaCl) was chosen rather than an initial IVCRI insulin dose of 0.045 U/kg/h because treatment with the higher dose has been associated with a better prognosis in cats with DKA.[1]

The type of fluid used for resuscitation has not been standardized in cats with DKA. Although 0.9% NaCl is recommended for the initial phase of fluid resuscitation and as long as hyponatremia is present in humans with DKA, the use of 0.9% NaCl has not been investigated in an original study of cats with DKA.[9] Similarly, protocols for correction of potassium, phosphate, and magnesium deficiencies in cats with DKA have not been established.

The objectives of this study were 3-fold. The first objective was to further characterize the use of IVCRI lispro for the treatment of DKA in cats in a randomized, controlled, blinded study in which cats received an initial IVCRI of lispro or regular insulin at a dose of 0.09 U/kg/h, and to compare the times to resolution of hyperglycemia, ketosis, and acidosis in cats treated with lispro and regular insulin IVCRI at this dose. The second objective was to characterize the use of 0.9% NaCl for fluid resuscitation and determine if this treatment is effective and safe in resolving hyponatremia in cats with DKA. The third objective was to explore new protocols for electrolyte supplementation in cats with DKA while using solutions with higher than previously reported electrolyte concentrations to correct low serum concentrations of potassium, phosphate, and magnesium. This study had 3 hypotheses. The first was that lispro insulin is effective and safe in treating DKA in cats and that resolution of hyperglycemia would be faster in cats treated with lispro insulin compared to those treated with the same dose of regular insulin. The second hypothesis was that 0.9% NaCl is effective and safe for treatment of hyponatremia in cats with DKA. The third hypothesis was that electrolyte supplementation with solutions that contain higher than previously reported electrolyte concentrations are effective and safe in correction of low serum concentrations of potassium, phosphate, and magnesium in cats with DKA.

2 | MATERIALS AND METHODS

2.1 | Study design

A prospective, randomized, controlled, blinded clinical study was performed. Client-owned cats with naturally occurring DKA were randomly assigned to receive either lispro or regular insulin IVCRI. Twelve sealed opaque envelopes containing either 1 of 6 "Lispro insulin" or 1 of 6 "Regular insulin" inserts were used, and the insulin assignment was known to nurses only, until the cat was discharged from the hospital or euthanized. Cats examined at a veterinary university hospital were enrolled between July 2011 and July 2013. Inclusion criteria were clinical signs suggestive of DM (polyuria, polydipsia, polyphagia, or weight loss), BG >300 mg/dL, serum B-hydroxybutyrate (BOHB) >2 mmol/L, venous pH <7.35, glucosuria on urine dipstick, and a signed owner consent form (which included consent for necropsy should the cat die or be euthanized during hospitalization). The study protocol and owner consent form were approved by the University's Institutional Animal Care and Use Committee. Cats were excluded if venous pH was <7.0 or if the owner did not consent. The study protocol called for exclusion of cats with a venous pH <7.0 because in dogs and humans with DKA, this pH is associated with death.[9,10] Ultimately, none of the cats were excluded from the study due to pH <7.0.

2.2 | Treatment protocol

Upon admission, all cats received IV fluid resuscitation with 0.9% NaCl. The initial fluid rate and bolus rate were determined by the emergency clinician based on the cat's body weight, estimated percentage of dehydration, estimated ongoing fluid losses, and maintenance fluid requirements. A fluid bolus was administered over a 20-minute time period if the cardiovascular system evaluation indicated that it was needed. Fluid boluses were not supplemented with electrolytes. The cardiovascular system evaluation included an assessment of the mucous membrane color, capillary refill time, heart rate,

pulse quality, and extremities' temperature. The cardiovascular status of each cat was reevaluated every 20-120 minutes depending on the rate of fluid administration and the initial cardiovascular system evaluation to determine the need for fluid rate adjustments.

The study protocol required that IVCRI of insulin begin after 6 hours of fluid resuscitation. However, the emergency room clinician was given discretion to deviate from the protocol as dictated by the clinical needs of each cat. Identical protocols were used for IVCRI of regular and lispro insulin, as described in Table 1. The initial dose of IVCRI insulin was 0.09 U/kg/h. Serum potassium concentration was corrected as described in Table 2. Serum potassium concentration was measured upon admission to the emergency room (Stat Profile; NOVA Biomedical Corporation, Waltham, Massachusetts), and correction of serum potassium deficiency was therefore started in the emergency room, if indicated. Phosphate was corrected by administering KPO_4 (3 mmol/mL PO_4 and 4.4 mEq/mL K^+) as an IVCRI at a rate of 0.06 mmol/kg/h if serum phosphate concentration was 2.0-2.9 mg/dL and at a rate of 0.12 mmol/kg/h if serum phosphate concentration was <2.0 mg/dL. Magnesium was corrected by administering $MgSO_4$ (500 mg/mL) as an IVCRI at a rate of 0.5 mEq/kg/24 h if serum magnesium concentration was 1.6-1.9 mmol/L and at a rate of 1 mEq/kg/24 h if serum magnesium concentration was <1.6 mmol/L. Serum phosphate and magnesium concentrations were measured within 24 hours of admission (Kodak Ektachem 250; Eastman Kodak Co, Rochester, New York) when the in-house clinical laboratory opened, and correction of phosphate and magnesium deficiencies was therefore started within 24 hours of admission, if indicated. The same broad-spectrum antibiotic treatment was administered to all cats in the form of ampicillin (22 mg/kg every 8 hours; Sandoz International GmbH, Holzkirchen, Germany) and enrofloxacin (5 mg/kg every 24 hours, Baytril; Bayer Healthcare, LLC, Shawnee Mission, Kansas). The protocol dictated that the same broad-spectrum antibiotic treatment be administered to all cats after cystocentesis was performed to obtain urine for an aerobic bacterial culture and sensitivity. This inclusion criteria was chosen because urinary tract infections are common in cats with DKA, and it was thought that clinicians would wish to treat cats for suspected infections, at least until results of the urine culture were obtained.[1] Broad antibiotic coverage was chosen to satisfy this clinical need and to maximize treatment uniformity. Additional medications including antiemetics, gastroprotectants, analgesics, and vasopressors were administered as deemed appropriate by the attending clinician.

TABLE 1 Protocol for IV continuous rate infusion of insulin in cats with diabetic ketoacidosis

Blood glucose concentration (mg/dL)	Fluid composition*	Rate of administration (mL/h)
>300	0.9% NaCl	10
200-300	0.9% NaCl + 2.5% dextrose	7
150-199	0.9% NaCl + 2.5% dextrose	5
100-149	0.9% NaCl + 5% dextrose	5
<100	0.9% NaCl + 5% dextrose	Stop insulin infusion

*2.2 U/kg of regular or lispro insulin (Humulin R or Humalog; Eli Lilly and Co, Indianapolis, Indiana) were added to a 250 mL bag of 0.9% NaCl. 10 mL were discarded from the bag before adding insulin. The bag was labeled by a nurse as containing insulin with no reference to regular or lispro insulin. The fluid line was flushed with 50 mL of insulin solution before starting the IV continuous rate infusion.

TABLE 2 Protocol for IV continuous rate infusion of potassium supplementation in cats with diabetic ketoacidosis

Serum potassium concentration (mmol/L)	Potassium (mEq/L, KCl) added to 250 mL bag of 0.9% NaCl*
<2.0	80
2.0-2.4	60
2.5-2.9	40
3.0-3.4	30
3.5-5.0	20

*Potassium supplementation never exceeded 0.5 mEq/kg/h. If KPO_4 was administered for phosphate supplementation, KCl supplementation was decreased accordingly.

2.3 | Definitions of resolution time of pronounced hyperglycemia, ketosis, and acidosis

The time of admission to the hospital was defined as the time an IV catheter was placed, and results of a first blood gas analysis were available for review (Stat Profile; NOVA Biomedical Corporation). Pronounced hyperglycemia was defined as a BG concentration ≥250 mg/dL. The time to resolution of pronounced hyperglycemia was defined as the time interval between admission and the time BG concentration was <250 mg/dL. The time to resolution of ketosis was defined as the time interval between admission and the time BOHB was <2.0 mmol/L. The time to resolution of acidosis was defined as the time interval between admission and the time venous pH was >7.35.

2.4 | Definitions of the time of SC insulin administration and duration of hospitalization

The time to SC insulin administration was defined as the time interval from admission until SC glargine was administered. Glargine was administered once acidosis had resolved and the cat was eating well. The IVCRI of insulin was discontinued 4-6 hours before the planned administration of SC glargine to ensure that the cat had some degree of hyperglycemia before glargine administration. The duration of hospitalization was defined as the time interval between admission and the time at which the cat was discharged from the hospital or euthanized.

2.5 | Evaluation for the presence of concurrent disorders

Data recorded in all cats at the time of admission included clinical signs, physical examination findings, and results of a CBC, serum biochemical profile, urinalysis, and aerobic urine bacterial culture and

sensitivity performed on urine obtained by cystocentesis before treatment with antibiotics (Celldyne 3500, Abbott Laboratories, Abbott Park, Illinois; Kodak Ektachem 250, Eastman Kodak Co; N-Multistix SG, Bayer Corporation, Elkhart, Indiana; Microscan WalkAway SI 40, Siemens Healthcare Diagnostics Inc, Sacramento, California). Serum sodium concentrations are reported as values corrected for hyperglycemia by adding 1.6 mmol/L to the measured sodium value for each glucose concentration of 100 mg/dL over 200 mg/dL.[11] Tests to be performed in all cats within 48 hours of admission included abdominal ultrasound, 3 view thoracic radiographs, antigen testing for feline leukemia virus (FeLV), antibody testing for feline immunodeficiency virus (FIV, FeLV antigen/FIV antibody test, IDEXX, Westbrook, Maine), thyroid hormone concentration, and feline pancreatic lipase immunoreactivity (PLI) measured as specific PLI quantification or SNAP PLI (Spec fPL [feline pancreas-specific lipase] assay or SNAP fPL assay; IDEXX). Imaging findings were interpreted by a board-certified radiologist, and ultrasonographic findings were defined as consistent with a diagnosis of acute pancreatitis if 2 of the 5 following abnormalities were identified: enlarged, irregular, or hypoechoic pancreas, hyperechoic peripancreatic mesentery, and peritoneal effusion. Pancreatic lipase immunoreactivity was considered abnormal if it was >3.5 μg/L on either test. Acute pancreatitis was diagnosed if cats had clinical signs and ultrasonographic findings consistent with the disease as well as an abnormal PLI. Insulin-induced hypoglycemia was defined as a BG concentration <60 mg/dL. Bradycardia was defined as a heart rate <160 bpm, and hypothermia was defined as a temperature <99.5°F.

2.6 | Monitoring

Blood glucose concentration was measured every 2 hours, and all reported values were measured with a point-of-care glucometer during the entire time that the cat received an IVCRI of insulin (AccuCheck Aviva; Roche Diagnostics Corp, Indianapolis, Indiana).[15] Serum sodium, potassium, and pH were measured from anaerobically handled and processed venous blood gas samples every 4-8 hours, and all reported values were measured with a point-of-care analyzer (Stat Profile; NOVA Biomedical Corporation). For each cat, the difference between the corrected sodium concentration at admission and the lowest corrected sodium concentration reached throughout the study was divided by the number of hours from admission to the time at which the lowest corrected sodium concentration was measured. Similarly, for each cat, the difference between the corrected sodium concentration at admission and the highest corrected sodium concentration reached throughout the study was divided by the number of hours from admission to the time at which the highest corrected sodium concentration was measured. These calculations were performed to determine the maximal rates of decrease or increase, respectively, in corrected sodium concentration for each cat. Blood BOHB was measured every 4-8 hours, and all reported values were measured using a portable ketometer (Precision Xtra; Abbott Diabetes Care Inc, Alameda, California). Serum phosphate and magnesium were measured at least every 24 hours but as often as every 6 hours as deemed appropriate by the attending clinician (Kodak Ektachem 250; Eastman Kodak Co). These values were used to adjust the rates of electrolyte supplementation. The median lowest BG was calculated in the following manner. First, the lowest BG documented in each cat throughout the study was identified. Second, the median of these values was calculated. The same calculation was performed for the median lowest and highest electrolyte concentrations.

2.7 | Statistical methods

Continuous variables were evaluated as not normally distributed because of the small number of cats included in this study. Results of descriptive statistics are therefore reported as the median (minimum, maximum). The Wilcoxon rank-sum test was used to compare variables between the 2 insulin treatment groups. The sign-rank test was used to compare BG at the time of admission to BG at the time the insulin IVCRI was started in all 12 cats. For all comparisons, a *P*-value <.05 was considered significant. All statistical evaluations were performed using a statistical software package (Stata 14.0 for Mac; Stata Corporation, College Station, Texas).

3 | RESULTS

Twelve cats were enrolled in the study. Six cats were randomized into the lispro insulin treatment group (LITG) and the other 6 cats were randomized into the regular insulin treatment group (RITG). Eighteen cats with confirmed DKA were excluded from the study during the study period. Ten of these 18 cats were euthanized at the time of admission at the request of their owners. Four cats were admitted for treatment but their owners refused to enroll the cat in the study, and 2 other cats were taken elsewhere for treatment. One cat was not enrolled because the hospital staff forgot to offer enrollment, and another cat was not enrolled because all the researchers were away at the time. Four additional cats with DM and suspected DKA were excluded because they did not meet all of the inclusion criteria. Three of these 4 cats had a BG <300 mg/dL and 1 cat had BOHB <2 mmol/L. Eight of the 12 study cats were discharged from the hospital and 4 (2 from each insulin treatment group) were euthanized. Data pertain to all 12 cats, except when specifically noted.

3.1 | Signalment, history, clinical signs, and physical examination findings

The median age of enrolled cats was 8 years (range 0.6-13 years). Eleven cats were domestic short-haired cats and 1 was a Maine Coon cat. Six cats were neutered males, 5 were neutered females, and 1 cat was an intact female. The median weight at discharge was 4.83 kg (range 2.48-6.37 kg).

Seven cats had newly diagnosed DM at the time of enrollment (3 in the LITG and 4 in the RITG). Five cats were diagnosed with DM and treated with SC insulin or an oral hypoglycemic agent before admission (3 in the LITG and 2 in the RITG). Two of these cats (1 in each treatment group) were treated with glargine insulin, 2 other cats from the LITG were treated with protamine zinc insulin or neutral

protamine Hagedorn insulin, and the fifth cat from the RITG was treated with glipizide. All insulin products and the glipizide were administered twice daily.

Clinical signs observed by the owner before admission into the hospital included decreased appetite or anorexia (9 cats), lethargy (8 cats), weight loss (7 cats), increased drinking and urination (7 cats), vomiting (5 cats), and weakness or incoordination (3 cats). Previously diagnosed medical conditions included DM (5 cats), and chronic pancreatitis, feline asthma, hypertrophic cardiomyopathy, hyperthyroidism, FIV positive status, upper respiratory infection, otitis, fungal nasal disease, and ceruminous gland adenocarcinoma, diagnosed in 1 cat each. In addition to insulin and glipizide, medications administered at the time of admission to the hospital included fluconazole, paroxetine, methimazole, mirtazapine, doxycycline, and a lysine supplement, administered to 1 cat each. Steroids were not given to any of the cats at the time of admission nor were they reported to have been given in the past.

At the time of admission, the most common physical examination abnormalities included dehydration (noted in 11 cats), lethargic mental status (8 cats), muscle wasting (7 cats), bradycardia (7 cats), and hypothermia (5 cats).

3.2 | Concurrent disorders

One cat, from the RITG, was euthanized within the first 24 hours of hospitalization and did not have imaging studies performed. Eleven of 12 cats had thoracic radiographs, which revealed hepatomegaly (in 10 cats), bronchial pattern (6 cats), cardiomegaly (4 cats), pleural effusion (1 cat), and bronchiectasis (1 cat). Abdominal ultrasound was performed in 11 of 12 cats and revealed hyperechoic small intestinal thickening (in 6 cats), hepatomegaly (5 cats), renomegaly (4 cats), and lymphadenopathy (3 cats). Two cats, both from the RITG, were diagnosed with acute pancreatitis.

There was no aerobic growth on the bacterial culture of urine collected via cystocentesis in any of the 12 cats. One cat was FIV positive, while the rest were FeLV and FIV negative. All cats had a thyroid hormone concentration <1 μg/dL. Abnormalities noted on CBC, biochemistry profiles, and urinalyses were similar to those previously reported in cats with DKA.[1]

Four cats (2 from each insulin treatment group) were euthanized during hospitalization and were not discharged from the hospital. Antemortem, all 4 cats had hypotension, 1 had pulmonary edema, and another was obtunded. They were euthanized at a median of 54 hours after admission (range 13-94 hours). All 4 cats had evidence of moderate to severe hepatic lipidosis on necropsy. Other necropsy findings included enteritis (3), pulmonary edema (2), adrenal necrosis and hemorrhage (2), necrotizing pancreatitis (1), and chronic tubular interstitial nephritis (1).

3.3 | Initial fluid treatment and initiation of IVCRI insulin

Initial fluid treatment consisted of a 20-minute fluid bolus in 11 of 12 cats. Six of these cats were in the LITG and 5 were in the RITG. The median fluid bolus rate given to cats in the LITG and RITG was 15 mL/kg/h (10-20 mL/kg/h) and 20 mL/kg/h (20-30 mL/kg/h), respectively. One cat in the RITG did not require a fluid bolus and received an initial fluid rate of 4 mL/kg/h. After the bolus, the median fluid rate given to 6 cats in the LITG and 5 cats in RITG was 5 mL/kg/h (4-7 mL/kg/h) and 4 mL/kg/h (4-6 mL/kg/h), respectively. Two cats (1 from each treatment group) received dopamine at 5-10 μg/kg/min or 12.5-15 μg/kg/min. These 2 cats were among the 4 cats that were euthanized.

The median time interval between admission time (when fluid resuscitation was initiated) until IVCRI of insulin began was 7.5 hours for the LITG (range 4-14 hours) and 7 hours for the RITG (range 6-9 hours). The median BG in all 12 cats at the time that IVCRI of insulin began was 344 mg/dL (175-579 mg/dL) and was significantly lower than the median BG at the time that fluid resuscitation was initiated (491 mg/dL, 300-698 mg/dL; $P = .008$).

3.4 | Adverse drug reactions

Local or systemic adverse effects associated with IV lispro insulin or IV regular insulin were not noted, except for insulin induced hypoglycemia. In the first 96 hours after admission 420 measurements of BG were performed; 177 in the LITG and 243 in RITG. One cat each from the LITG and RITG developed hypoglycemia at 68 and 94 hours after admission, respectively. The lowest BG measured for each of these cats was 40 mg/dL, and no clinical signs associated with the hypoglycemia were recorded in either cat. No other events of hypoglycemia were recorded throughout the study in any of the cats. The median lowest BG recorded throughout the study in the LITG was 151 mg/dL (40-284 mg/dL) and was significantly higher than the median lowest BG in the RITG (108 mg/dL [40-139 mg/dL]; $P = .04$).

3.5 | Resolution of hyperglycemia, ketosis, and acidosis

Median BG concentration, BOHB concentration, and pH at the time of admission to the hospital and during the first 96 hours of hospitalization are reported in Table 3. Some of the reporting related to BG, ketosis, and acidosis is limited to the first 96 hours of hospitalization because most of these variables normalized within this time frame. The median times to resolution of hyperglycemia, ketosis, and acidosis are also reported in Table 3.

3.6 | Time of SC insulin administration and duration and cost of hospitalization

The median time to administration of SC glargine, in 8 cats, was not significantly different between the LITG (74 hours, 30-104 hours) and RITG (56 hours, 30-80 hours). The median duration of hospitalization in 12 cats was also not significantly different between the LITG (64 hours, 13-132 hours) and RITG (94 hours, 51-112 hours). Furthermore, the median cost of hospitalization in 12 cats was not significantly different between the LITG (3386 US dollars, 847-5848 US dollars) and RITG (3204 US dollars, 1480-5970 US dollars).

TABLE 3 Median blood glucose (BG) concentration, beta-hydroxybutyrate (BOHB) concentration, and venous pH at the time of admission to the hospital and during the first 96 hours of hospitalization, and median times to resolution of hyperglycemia, ketosis, and acidosis

	BG (mg/dL)		BOHB (mmol/L)		Venous pH	
Insulin type	**Lispro**	**Regular**	**Lispro**	**Regular**	**Lispro**	**Regular**
Number of samples measured in the first 96 hours of hospitalization	420		141		140	
	177	243	62	79	63	77
Median (range) concentration at admission	467 (300-698)	546 (378-627)	8 (3.2-8)	8 (6.9-8)	7.25 (7.14-7.32)	7.22 (7.17-7.37)
Median (range) concentration during first 96 hours of hospitalization	229 (117-448)	247 (144-283)	5.7 (2.2-7.3)	4.2 (1.5-6.3)	7.32 (7.20-7.35)	7.33 (7.19-7.40)
Median (range) hours to biochemical resolution (BG <250 mg/dL, BOHB >2.0 mmol/L, pH >7.35)**	7 (2-10)*	12.5 (8-20)*	60 (18-80)	68 (18-92)	32 (10-40)	30 (18-62)

None of these values were significantly different between the lispro and regular insulin treatment groups, except where noted.
*P = .02.
**Data pertain to 6 lispro-treated cats and 6 regular insulin–treated cats, except when specifically noted. Pronounced hyperglycemia resolved in 11 of 12 cats (5 in the lispro insulin treatment group [LITG] and 6 in the regular insulin treatment group [RITG]). One cat in the LITG was euthanized 13 hours after admission with a BG of 289 mg/dL before pronounced hyperglycemia resolved. Ketosis resolved in 9 of 12 cats (5 in the RITG and 4 in the LITG). Three other cats were euthanized before resolution of ketosis. Acidosis resolved in 5 of 6 cats in each treatment group. Two other cats were euthanized before resolution of acidosis.

3.7 | Electrolyte concentrations

Electrolyte concentrations are reported in Table 4. The maximal rate of increase or decrease in corrected sodium concentration was noted in a cat in the RITG as corrected sodium declined to its lowest reading throughout the study at a rate of 0.7 mmol/L/h. Of note are 3 cats. One cat from the LITG, in which the phosphate concentration reached 12.6 mg/dL, was never treated with phosphate supplementation because it at no time had hypophosphatemia. A second cat in the LITG developed a low phosphate concentration of 0.6 mg/dL. The cat was not receiving phosphate supplementation when it developed this hypophosphatemia because the previous phosphate measured 16 hours earlier was 3.2 mg/dL. Once the phosphate concentration of 0.6 mg/dL was documented, phosphate supplementation began, and phosphate concentrations measured 10 and 24 hours after supplementation began were 1.9 and 7.8 mg/dL, respectively. Phosphate supplementation was discontinued 24 hours after it began. A third cat from the LITG developed hyperkalemia of 6.8 mmol/L after 116 hours of hospitalization, after the lispro IVCRI had been discontinued, after glargine treatment had begun, once the cat was eating, and just before the cat was discharged to go home. At the time that hyperkalemia of 6.8 mmol/L developed, the cat was receiving 1 mL/kg/h of IV fluids supplemented with potassium as per Table 2 because potassium concentration measured 12 hour earlier was 3.7 mmol/L. During the cat's hospitalization, it had 21 additional potassium measurements that ranged from 2.4-4.2 mmol/L.

4 | DISCUSSION

The median time to resolution of initial pronounced hyperglycemia was significantly shorter in the LITG compared with the RITG. However, when focusing on the lowest BG measured in each of the cats throughout the study, it was noted that the median lowest BG in the LITG was significantly higher than the median lowest BG in the RITG. It was therefore concluded that in cats with DKA, lispro insulin leads to a faster resolution of initial pronounced hyperglycemia, with less overall risk of hypoglycemia compared to regular insulin. However, larger studies including more cats with hypoglycemia are needed to further investigate these findings and potential conclusion.

Faster resolution of initial pronounced hyperglycemia with less overall risk of hypoglycemia has also been documented in humans with critical illness and is attributed to the rapid onset of action and shorter duration of action of lispro when compared to regular insulin.[7] Lispro's short onset of action could have contributed to a faster resolution of initial pronounced hyperglycemia in the LITG compared to the RITG. Lispro's short duration of action means that when lispro insulin is discontinued, or when its dose is reduced, its lingering effect on BG concentration is dampened quickly, and as a result, it is less likely to cause hypoglycemia in comparison to regular insulin.

Despite the faster resolution of pronounced hyperglycemia in the LITG, an analysis of over 400 BG measurements in the first 96 hours of treatment indicated that overall glycemic regulation was similar in the 2 treatment groups. Larger studies are needed to determine if the faster resolution of pronounced hyperglycemia in the LITG is clinically important. Insulin-induced hypoglycemia occurred in 1 cat in each treatment group, and no clinical signs were observed in association with the hypoglycemia. This frequency of hypoglycemia is consistent with other reports of insulin-induced hypoglycemia in cats with DKA.[4,5]

A case series describing the use of lispro and regular insulin in 15 cats with DKA found that lispro was safe and effective at a starting IVCRI dose of 0.045 U/kg/h.[5] However, a different retrospective study of 93 cats with DKA treated with regular insulin found that cats treated with an initial IVCRI dose of 0.09 U/kg/h had a better outcome compared to cats treated with an initial IVCRI dose of 0.045 U/kg/h.[1] Therefore, the protocol of the study reported here was designed to begin the lispro and regular insulin IVCRI at a dose of 0.09 U/kg/h. The

TABLE 4 Serum electrolyte concentrations in cats with diabetic ketoacidosis treated with IV continuous rate infusion of lispro or regular insulin

	Corrected serum sodium concentration, median (range); reference range, 146-157 mmol/L*		Serum potassium concentration, median (range); reference range, 3.5-4.8 mmol/L		Serum magnesium concentration, median (range); reference range, 1.9-2.6 mg/dL		Serum phosphate concentration, median (range); reference range, 3-6.6 mg/dL	
	Lispro	**Regular**	**Lispro**	**Regular**	**Lispro**	**Regular**	**Lispro**	**Regular**
Number of cats	6	6	6	6	NA	NA	NA	NA
At admission	148 (143-149)**	156 (147-162)**	2.7 (2.5-3.5)***	3.3 (3.1-4.1)***	NA	NA	NA	NA
Number of cats above reference range at admission	None	3	None	None	NA	NA	NA	NA
Number of cats below reference range at admission	2	None	5	4	NA	NA	NA	NA
When IVCRI insulin began	149 (141-154)	154 (141-157)	2.9 (2.6-3.4)	3.4 (3.1-4.1)	NA	NA	NA	NA
Number of samples collected throughout entire study	n = 157		n = 160		n = 56		n = 57	
	Lispro n = 74	**Regular n = 83**	**Lispro n = 77**	**Regular n = 83**	**Lispro n = 28**	**Regular n = 28**	**Lispro n = 28**	**Regular n = 29**
Median lowest throughout study (after admission)	141 (127-149)	145 (135-149)	2.4 (2.3-2.7)	2.7 (2.1-2.8)	1.5 (1.2-1.9)	1.2 (1.0-1.8)	2.6 (0.6-4.2)	2.6 (1.5-5.1)
Hours from admission (for median lowest concentration)	3.5 (0-28)	27 (18-44)	21 (0-50)	28 (10-38)	22 (18-88)	30 (6-86)	24 (18-48)	26 (6-42)
Median highest throughout study (after admission)	154 (150-157)	155 (145-159)	3.6 (2.6-6.8)	4.1 (3.5-6.0)	2.5 (2.2-3.7)	2.4 (1.7-4.2)	7.4 (5.6-12.6)§	4.7 (3.9-5.9)§
Hours from admission (for median highest concentration)	21 (6-80)	3 (0-48)	28 (0-124)	24 (6-106)	Zero (0-18)	14 (0-106)	46 (0-92)	Zero (0-106)
Number of cats above reference range throughout entire study	None	2	2	1	2	2	3	None
Number of cats below reference range throughout entire study	5	4	6	6	4	6	3	5

None of the values are significantly different between the lispro and regular insulin treatment groups, except where noted.
Serum phosphate and magnesium concentrations were measured within 24 hours of admission when the in-house clinical laboratory opened.
Abbreviation: IVCRI, IV continuous rate infusion; NA, not applicable.
*Serum sodium concentrations were corrected for hyperglycemia by adding 1.6 mmol/L to the measured sodium value for each 100 mg/dL blood glucose concentration over 200 mg/dL.
**P = .02.
***P = .04.
§P = .01.

findings of this study augment the findings of the case series involving lispro treatment in cats with DKA in that it can now be concluded that lispro insulin is a safe and effective treatment for cats with DKA at a starting dose of 0.09 U/kg/h. Given these findings, it is recommended that IVCRI lispro treatment in cats with DKA begin at a dose of 0.09 U/kg/h.

When analyzing the BG in all 12 cats, a significant decrease in BG concentration was detected between the time that fluid resuscitation was initiated and IVCRI of insulin began. It is therefore concluded that fluid resuscitation alone is effective in significantly decreasing BG during the first 7 hours of treatment. This finding, which has also been reported in dogs, raises a concern that early treatment with IVCRI of insulin, before 7 hours of fluid resuscitation, could cause too rapid a decrease in BG concentration as the effects of fluid resuscitation and insulin are combined to decrease BG.[8] This concern over early IVCRI of insulin administration is different than the conclusion reached in a retrospective study which concluded that early insulin treatment (within the first 6 hours of hospital admission) resulted in faster resolution of ketonuria compared to when insulin was given after 6 hours of admission.[13] However, because of the retrospective nature of the study, it is not known why some patients received insulin later than others. It is possible that patients with severe morbidity received insulin later than others, and due to this severe morbidity had later resolution of ketonuria, which was unrelated to the time at which the insulin treatment began.[13]

It is important to note that the more rapid resolution of hyperglycemia observed in the LITG compared to the RITG is probably not associated with the eventual outcome of the patient. The median time to administration of SC insulin and median duration of hospitalization are likely better indicators of overall treatment success. These times were not significantly different between the LITG and the RITG. It was therefore concluded that in cats with DKA, lispro can be used as an efficient and safe alternative to regular insulin. However, the overall outcome of DKA treatment in cats is unlikely to be different with the use of lispro or regular insulin.

The same fluid type, 0.9% NaCl, was administered for fluid resuscitation, maintenance fluid therapy, and as a vehicle for IVCRI insulin administration in all cats. This is the first such use of 0.9% NaCl reported in an original study of cats with DKA. Original studies of DKA treatment in cats have not reported the type of fluid used for resuscitation or reported more than 1 fluid type for this purpose. [3-5,13,14] One study did report using 0.9% NaCl only for IVCRI insulin administration, similar to the protocol used in this study.[3]

The protocol for IVCRI insulin administration reported in most studies is based on a study of dogs with DKA.[15] In the dog study, it was recommended that IVCRI insulin administration begin with 0.9% NaCl and be switched to 0.45% NaCl with dextrose when BG dropped below 250 mg/dL.[15] This recommendation is technically laborious and could have been made due to concerns over hypernatremia. The results of this study support the continued use of 0.9% NaCl for both fluid resuscitation and IVCRI insulin administration. The highest corrected sodium concentration reported after 0.9% NaCl resuscitation began was 159 mmol/L, and this mild hypernatremia was documented in only 2 cats. The median highest corrected sodium concentrations remained within the reference range. Hyponatremia, on the other hand, was more common and more severe. It developed or was maintained in 9 cats, and the median lowest corrected sodium concentrations recorded throughout the study were below the reference range. Although there were significant differences in the corrected sodium concentration between the LITG and the RITG at the time of initial examination, these differences resolved with 0.9% NaCl treatment. The hourly change in corrected sodium concentration never exceeded 1 mmol/L/h. It is therefore concluded that 0.9% NaCl is a suitable initial fluid choice for both resuscitation and IVCRI insulin administration in cats with DKA. However, randomized controlled clinical trials comparing outcomes of treatment in cats with DKA treated with different fluid types are needed to substantiate the findings reported in this study.

Protocols for potassium supplementation in cats with DKA are either not described or utilize a protocol established for dogs with DKA.[3-5,13-15] However, cats require different electrolyte supplementation protocols with higher electrolyte concentration solutions because the total volume of fluid infused to cats is smaller than that administered to dogs. With this in mind, new protocols for potassium, magnesium, and phosphate supplementation for cats with DKA were used in this study. Despite the higher concentration of potassium solution used for treatment, all cats maintained or developed hypokalemia at some point throughout the study. However, the hypokalemia was mild, indicating that this potassium supplementation protocol is effective.

Despite the higher potassium infusion rates in this study, hyperkalemia was uncommon. Hyperkalemia was documented in only 3 cats 1 of which developed a hyperkalemia of 6.8 mmol/L. However, hyperkalemia can be fatal. Therefore, cats receiving high fluid rates with potassium supplementation should have potassium concentration measured hourly and potassium supplementation recalculated accordingly, to avoid the risk of hyperkalemia.

This study has several limitations. First, it is a small study, which was undertaken to ascertain the safety and effectiveness of a new lispro insulin IVCRI protocol. Another limitation is that cats with DKA have concurrent illness.[1] Therefore, response to treatment and electrolyte concentrations were likely influenced not only by treatment protocols but also by the presence of concurrent diseases. Additionally, the protocol required that IVCRI of insulin begin after 6 hours of fluid resuscitation. However, the emergency room clinician was given latitude to deviate from the protocol and IVCRI of insulin was begun up to 14 hours after fluid resuscitation was initiated. It is not known why some cats had IVCRI insulin introduced later than others. Possible explanations could include the busy and unpredictable setting of an emergency room, ongoing conversations with the owners about the decision to treat or enroll in the trial, and the cardiovascular status of the cat. The effect of these limitations on the study findings is not known.

In conclusion, IVCRI lispro insulin administered at an initial dose of 0.09 U/kg/h is safe and effective for treatment of DKA in cats. Should regular insulin become unavailable, or if lispro insulin becomes more competitively priced, lispro insulin is a reasonable option for IVCRI treatment of cats with DKA. Additionally, 0.9% NaCl is effective and

safe for treatment of hyponatremia in cats with DKA. Finally, electrolyte supplementation with solutions that contain higher than previously reported electrolyte concentrations are effective and safe for correction of potassium, phosphate, and magnesium deficiencies in cats with DKA. Larger future studies can build on these findings to further validate or modify the treatment protocols reported here.

ACKNOWLEDGMENT

Presented as an abstract at the 2018 American College of Veterinary Internal Medicine Forum, Seattle, Washington.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study protocol and owner consent form were approved by the University of Pennsylvania. IACUC.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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How to cite this article: Anderson JD, Rondeau DA, Hess RS. Lispro insulin and electrolyte supplementation for treatment of diabetic ketoacidosis in cats. *J Vet Intern Med*. 2019;33: 1593–1601. https://doi.org/10.1111/jvim.15518