Retrospective Study

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Comparison of regular insulin infusion doses in critically ill diabetic cats: 29 cases (1999–2007)

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Abstract

Objective – To compare biochemical parameters, neurologic changes, length of hospital stay, and clinical improvement in 3 groups of cats with diabetic ketosis/diabetic ketoacidosis (DK/DKA) prescribed varied doses of regular insulin as a continuous rate of infusion (CRI).
Design – Retrospective study.
Setting – University teaching hospital.
Animals – Twenty-nine client-owned cats with DK/DKA prescribed a regular insulin CRI.
Interventions – Cats were grouped as follows: 7 cats each in Group 1 and 2, (prescribed 1.1 and 2.2 U/kg/d, respectively), and 15 cats in Group 3 (prescribed increasing doses as needed).
Measurements and Main Results – None of the groups received the total prescribed dose of insulin. The mean actual dose administered/kg/d ranged from 0.30 (0.21) to 0.87 (0.32) U/kg/d in Groups 1, 2, and 3. There was no difference in mean minimum blood glucose (BG) per 4 hours or change in BG from baseline per 4 hours between Groups 1 and 2 ($P = 0.63$, 0.50). There was no difference between groups regarding the time required to reach a BG $\leq$ 13.9 mmol/L (250 mg/dL), serum phosphorus or potassium concentrations relative to baseline values ($P = 0.53$, 0.90), length of time until urine or serum ketones were no longer detected ($P = 0.73$), the animal commenced eating ($P = 0.24$), or length of hospital stay ($P = 0.63$). Four of the cats had declining mentation during hospitalization; there were no relationships between osmolality at presentation, either prescribed or administered insulin dose, and mentation changes. Three of the 4 cats with declining mentation survived. Twenty-seven of the 29 cats (93%) survived to discharge.
Conclusions – In this study, prescribing the published canine dose (2.2 U/kg/d) of regular insulin to cats with DK/DKA does not appear to increase the frequency of adverse neurologic or biochemical sequelae compared with cats that are prescribed the published cat dose (1.1 U/kg/d). The use of a sliding scale for determination of infusion rates significantly reduces the amount of insulin cats receive in this setting. Determination of whether adverse sequelae would occur more frequently if cats with DK/DKA received the full insulin prescribed doses of 1.1, 2.2, or $>$2.2 U/kg/d is warranted. Further controlled studies are necessary to determine if higher doses of insulin are associated with beneficial effects on morbidity or mortality.

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Introduction

Diabetes mellitus (DM) is an uncommon disease affecting about 1 in 400 cats.[1] Diabetic ketosis (DK) and diabetic ketoacidosis (DKA) are serious complications seen primarily in previously undiagnosed diabetics or newly diagnosed, but poorly controlled diabetics.[2–5] Commonly seen abnormal clinical and laboratory findings in cats with DK/DKA include severe dehydration (occasionally accompanied by hypovolemia), mental obtundation, acid-base and electrolyte disturbances, and hyperosmolality.[2,3,5–8] Therapy commonly includes isotonic crystalloids, potassium, phosphorus, and magnesium supplementation, and conservative doses of exogenous regular crystalline insulin to decrease the blood glucose (BG) approximately 2.8 mmol/L/h (50 mg/dL/h) until a BG less than the feline renal threshold for glucose ($\leq$ 13.9 mmol/L, $\leq$ 250 mg/dL) is reached.[5,6,9] Aggressive insulin administration may

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lead to precipitous declines in BG, resulting in cerebral edema, hypokalemia, hypomagnesemia, or hypophosphatemia.[6,9,10] Insulin administration is required to abate lipolysis, the hepatic production of ketone bodies and glucose, as well as to promote tissue uptake and metabolism of glucose.[9,11] Insulin administration is often not initiated until intravenous (IV) fluids have been administered for 2–4 hours as IV fluids alone will decrease the BG by decreasing catecholamine concentrations and increasing glomerular filtration rate.[6,12]

The recommended insulin type for the management of DK/DKA is regular crystalline insulin as it has a rapid onset of action and a short half life.[5] It can be administered IV as a continuous rate infusion (CRI), or as intermittent intramuscular or subcutaneous injections. The subcutaneous route is not recommended until the patient has been rehydrated as absorption from the subcutaneous space in a dehydrated animal can be unpredicatable.[5,6]

A CRI dose of 1.1 U/kg/d of regular insulin has been published in textbooks and in the veterinary literature for cats, but no prospective studies have been performed to evaluate the effectiveness of this dosing protocol in this species.[5,6,13] A prescribed CRI dose of 2.2 U/kg/d of regular insulin has been prospectively evaluated in dogs with DKA.[14] It appears a lower prescribed dose of regular insulin was chosen for cats because, in 1 author's experience, cats with DKA had a higher blood osmolality on presentation than dogs with DKA.[6] The lower prescribed insulin dose would theoretically decrease the BG and blood osmolality less rapidly, and thus decrease the risk of cerebral edema formation.[6]

The objective of this study was to retrospectively compare biochemical parameters, neurological function, and duration of care in 3 groups of cats with DKA presenting to a university teaching hospital emergency room between 1999 and 2007. These 3 groups were prescribed a regular insulin CRI at 1.1 U/kg/d (Group 1), 2.2 U/kg/d (Group 2), or initiated on 1.1 U/kg/d with subsequent dose escalation to $\geq$ 2.2 U/kg/d during the course of therapy (Group 3).

Materials and Methods

The study population consisted of cats admitted to a university teaching hospital between the years 1999 and 2007 that were diagnosed with DK or DKA and treated with a documented IV regular insulin CRI. Cats were excluded if the dose of insulin was not recorded in the medical record or if the cat received $<$2 hours of the insulin infusion. In the case of multiple visits by 1 cat for the problem of DK/DKA, data were only included for the first visit as the data from subsequent visits could not be treated as wholly independent from that of the first visit.

Cats were considered to have DK/DKA if they had a BG $>$ 13.9 mmol/L (250 mg/dL) and ketones were detected in the urine or serum. No distinction was made between cats with DK and cats with DKA for the purpose of this study.

Medical records were reviewed and data were collected for retrospective analysis. Data collected included signalment, presenting complaint, and prior medical history including date on which the diagnosis of DM was first made and length of time between diagnosis of DM and presentation with DK/DKA. Physical examination findings on presentation were recorded including level of mentation, rectal temperature, heart rate, respiratory rate, body condition, and body weight. Hypothermia, bradycardia, and tachypnea were defined as follows: a rectal temperature below 37.8°C (100°F), a heart rate less than 160/min, and a respiratory rate greater than 40/min.

On presentation, venous blood pH, bicarbonate, glucose, sodium, potassium, and BUN concentrations were determined using a blood gas analyzer.[a] Total osmolality was calculated from laboratory parameters measured in US conventional units and applying the following equation: $Osm_{calc} = 2(Na+K)+(BG/18)+(BUN/2.8)$.[15] When urine was easily obtained, urine ketones were assessed using colorimetric, semi-quantitative urine test strips.[b] When urine was unavailable, plasma ketones were measured using a colorimetric, semi-quantitative urine test strip[b] method that has been validated previously.[16] During the course of hospitalization, BG concentrations were assessed every 2 hours using a bedside glucometer or a blood gas analyzer.[c,d] Blood electrolytes including sodium, potassium, and bicarbonate were assessed every 4–12 hours using a blood gas analyzer or a laboratory blood chemistry analyzer.[d,e] Phosphorus and magnesium concentrations were measured once daily using a laboratory blood chemistry analyzer.[e] Ketones were re-assessed in the urine or plasma daily using colorimetric, semi-quantitative urine test strips.[b]

All cats received IV fluids separately from the insulin CRI. The insulin CRI consisted of 240 mL of 0.9% NaCl to which the total daily dose of regular crystalline insulin was added.[f] Fifty milliliters of the solution was run through the tubing to saturate nonspecific binding sites.[17] BG concentrations were measured every 2 hours and a sliding scale was used to adjust the IV insulin infusion rates from 0 to 10 mL/h (with dextrose supplementation if indicated) based on current BG values. The BG values at which insulin CRI rates were to be altered or dextrose supplementation to be initiated (or

withdrawn) were implemented at the individual clinician's discretion in each case.

The patient data were entered into a computer spreadsheet program.[g] Data entered included information detailed above, time of IV insulin CRI initiation, rate of insulin CRI administration, and daily prescribed dose of insulin for each cat. BG concentration, insulin CRI rate changes, and insulin CRI daily prescribed dose changes were entered every 2 hours or when they occurred during the first 72 hours of insulin CRI administration. When the BG concentration was recorded in the medical record as 'high', the maximum limit of BG detection by the glucometer (33.3 mmol/L, 600 mg/dL) was substituted for purposes of data analysis. Total daily insulin dose received was calculated as follows: [24 h dose of insulin CRI (mL) × concentration of insulin solution (U/mL)]/patient body weight (kg).

Five serum bicarbonate and 5 serum potassium measurements that were obtained 6–8 hours apart were entered for the first 48 hours of IV insulin CRI administration. Where available, phosphorus and total magnesium concentrations were entered every 24 hours for the first 4 days of therapy. Additional data entered into the computer spreadsheet program included number of hours the patient received IV crystalloid fluids before initiating IV insulin CRI, hours until the BG was $\leq$ 13.9 mmol/L (250 mg/dL), hours until urine or plasma tested negative for ketones, days until the IV insulin CRI was discontinued, presence of declining mentation or seizures during hospitalization, presence or absence of bicarbonate supplementation, hours until initiation of voluntary eating, concurrent diseases diagnosed, total length of hospitalization, and outcome (survived, euthanized, or died).

After the initial analysis revealed that the 3 different approaches to insulin infusions [(1) feline standard: 1.1 U/kg/d prescribed, (2) canine standard: 2.2 U/kg/d prescribed, and (3) escalating dosage] resulted in comparable mean daily doses of insulin actually being administered, a post hoc analysis based on actual insulin administered (rather than prescribed) was undertaken. This analysis was not part of the original design and was initiated solely in a post hoc manner. The 29 patients were ranked according to mean daily insulin dose received and the 10 cats that received the lowest and the 10 cats that received the greatest quantity of insulin (U/kg/d) were stratified into separate groups for further analysis. The 9 remaining cats that received intermediate daily insulin doses were excluded from the post hoc analysis. The groups were compared for differences in the following parameters: daily insulin dose received, days of hospitalization, percent mortality, and percent in which declining mentation was detected.

Data analysis

The cats were divided into 3 separate groups for data analysis. Group 1 included cats that were prescribed 1.1 U/kg/d of regular insulin as a CRI. Group 2 included cats that were prescribed 2.2 U/kg/d of regular insulin as a continuous rate infusion. In both Groups 1 and 2 the rate of administration changed as described above according to the BG-dependent sliding scales used in study institution, but the concentration of the insulin infusion remained the same throughout the duration of treatment. Group 3 included cats that initially were prescribed 1.1 U/kg/d of regular insulin as a CRI and, during the course of their stay, the concentration of the insulin CRI increased to $\geq$ 2.2 U/kg/d. As with Groups 1 and 2 the rate of administration ranged from 0 to 10 mL/h and was adjusted using a sliding scale based on the BG measurement obtained every 2 hours.

Average minimum BG concentration per 4 hours and change in BG concentration from baseline per 4 hours was measured in all 3 groups, starting once the insulin CRI was initiated, and extending through 36 hours (all cats were receiving an insulin CRI up to this point). To determine differences between groups 1, 2, and 3, analysis of variance in repeated measures was used.

To determine differences between Groups 1, 2, and 3 with regard to physical examination findings, presenting blood work values, time until BG $\leq$ 13.9 mmol/L (250 mg/dL), total daily administered doses of insulin (U/kg/d), time until insulin CRI was discontinued, and length of hospitalization, analysis of variance was performed. Post hoc pairwise comparisons were accomplished using the *t*-test. To examine changes over time in phosphorus, potassium, and bicarbonate concentrations among the 3 groups, analysis of variance in repeated measures was performed. In the majority of cats, multiple data points for magnesium were missing; therefore analysis of magnesium values was not performed. Time until clearance of urine or plasma ketones and hours until the patient commenced eating was examined by the Kruskal-Wallis test. The relationship between declining mentation status and blood osmolality was examined by linear regression. Correlation of osmolality to hours of IV fluids received before initiating insulin CRI was examined via linear regression. Presence of declining mentation status and osmolality was compared using the Student's *t*-test.

In the post hoc analysis, mean daily insulin dose received and days of hospitalization were examined using Student's *t*-test after normal distribution of the data was confirmed using the Shapiro-Wilk test. Percent mortality and percent in which declining mentation was detected was examined using the Fisher Exact Test due to the rarity of these events within the study groups.

All analyses were performed using either SAS statistical software, or Sigmaplot 11.[h,i] Significance levels for multiple comparisons were adjusted for using Bonferroni's correction and significance was set at a P value of <0.005. For the post hoc analysis (in which multiple comparisons were not made), a standard uncorrected P value of 0.05 was used. Categorical data are presented as frequencies and percents. Continuous data is presented as mean (SD) for parametric data and median and interquartile ranges (IQR) for nonparametric data.

Results

Thirty-three medical records comprising 39 total visits for treatment of DKA were evaluated initially. Three cats were excluded because the daily insulin dose was not recorded in the medical record. One cat was excluded because it died after 1 hour of initiating insulin CRI therapy. Four cats had a total of 6 repeat visits that were excluded from analysis, leaving a total of 29 cats included in the study.

There were 7 cats in Group 1, 7 cats in Group 2, and 15 cats in Group 3. There was no significant difference between groups with regards to the mean age, breed, and sexual status (neutered or intact). Previously diagnosed diabetics comprised 41.4% of the population with 3 cats each in Groups 1 and 2, and 6 cats in Group 3. These cats had been diagnosed with DM a median of 16 months (IQR: 4.25–34.5 months) before presentation with DK/DKA. Presenting complaints included lethargy (93.1%, 27/29), anorexia (89.7%, 26/29), vomiting (65.5%, 19/29), weight loss (62.1%, 18/29), and polyuria and/or polydipsia (58.6%, 17/29, Table 1).

Physical examination of all cats at the time of presentation revealed the following: dehydration (96.6%, 28/29), mentation changes (69%, 20/29 obtunded; 20.7%, 6/29 stuporous), hypothermia (44.8%, 13/29), bradycardia (48.3%, 14/29), tachypnea (13.8%, 4/29), overweight body condition (20.7%, 6/29), underweight body condition (55.2%, 16/29). Cats in Group 2 were more likely to be underweight and hypothermic compared with cats in Groups 1 and 3 but these differences were not statistically significant (Table 2). Cats in Group 2 had a lower mean heart rate than cats in Groups 1 and 3, but again this difference did not achieve statistical significance [heart rate = 142 (13) versus 174 (16) versus 168 (25), respectively, $P = 0.025$]. All but 1 cat with DK/DKA had concurrent disease(s) or clinical abnormalities diagnosed via abdominal ultrasound or laboratory testing.

Table 1: The five most common presenting complaints in cats with diabetic ketosis/diabetic ketoacidosis presented to the teaching hospital between 1999 and 2007

	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)
Lethargy	6 (85.7)	7 (100)	14 (93.3)
Anorexia	6 (85.7)	6 (85.7)	14 (93.3)
Vomiting	4 (57.1)	4 (57.1)	11 (73.3)
Weight loss	3 (42.9)	5 (71.4)	10 (66.7)
PU/PD	4 (57.1)	4 (57.1)	9 (60.0)

Group 1: cats prescribed a regular insulin CRI at 1.1 U/kg/day; Group 2: cats prescribed a regular insulin CRI at 2.2 U/kg/day; Group 3: cats initially prescribed a regular insulin CRI at doses starting at 1.1 U/kg/day, but which required greater insulin administration to address hyperglycemia.

Table 2: Common physical examination findings in cats with diabetic ketosis/diabetic ketoacidosis presenting to the teaching hospital between 1999 and 2007

	Group 1 (*n* = 7)	Group 2 (*n* = 7)	Group 3 (*n* = 15)	*P*-value
Rectal Temp (°F)	100.5 ± 1.3	97.7 ± 4.4	100.2 ± 2.3	0.15
HR (beats/min)	174 ± 16	142 ± 13	168 ± 25	0.025
RR (breaths/min)	38 ± 18	28 ± 9	30 ± 11	0.36
Body weight (kg)	5.4 ± 1.8	4.2 ± 2.1	4.2 ± 1.2	0.31
Overweight	2 (28.6%)	1 (14.3%)	3 (20.0%)	N/A
Underweight	2 (28.6%)	5 (71.4%)	9 (60.0%)	N/A
Dehydrated	6 (85.7%)	7 (100.0%)	15 (100.0%)	N/A
Obtunded	6 (85.7%)	6 (85.7%)	8 (53.3%)	N/A
Stuporous	0 (0.0%)	1 (14.3%)	5 (33.3%)	N/A

Data are presented as mean ± standard deviation or number of cats with percentage of that group's population represented. No statistically significant differences between groups for rectal temperature, heart rate, respiratory rate, and body weight were noted. No statistical comparisons were performed between the groups for the last 5 parameters listed in the table. Group 1: cats prescribed a regular insulin CRI at 1.1 U/kg/day; Group 2: cats prescribed a regular insulin CRI at 2.2 U/kg/day; Group 3: cats initially prescribed a regular insulin CRI at doses starting at 1.1 U/kg/day, but which required greater insulin administration to address hyperglycemia.
HR, heart rate; RR, respiratory rate.

Cats in Groups 2 and 3 were acidotic, with Group 2 having the lowest mean pH [7.24 (0.11)] of all 3 groups, however, this difference was not statistically significant ($P = 0.2$). There were no statistically significant differences between the 3 groups regarding the concentrations of BG, sodium, potassium, BUN, and serum osmolality on presentation (Table 3). The blood bicarbonate concentration on presentation was higher in Group 1 compared with Group 2, but the difference was not statistically significant ($P = 0.03$).

On presentation, only 2 of 29 cats had a calculated serum osmolality less than 305 mOsm/L. Of all cats, 44.8% (13/29) had a calculated total serum osmolality > 350 mOsm/L. Of these cats, 92.3% (12/13) had either obtunded or stuporous mentation on presentation. Of the entire study population, 4 cats had declining mentation status during the course of hospitalization. The total daily insulin dose administered to

Table 3: Laboratory values on presentation in cats presenting to our hospital with diabetic ketosis/diabetic ketoacidosis between 1999 and 2007

	Group 1 ($n = 7$)	Group 2 ($n = 7$)	Group 3 ($n = 15$)	*P*-value
Blood glucose (mg/dL) (67–168 mg/dL)	397 ± 117	405 ± 159	466 ± 161	0.52
Sodium (mmol/L) (146–157 mmol/L)	145 ± 4	145 ± 9	150 ± 8	0.31
Potassium (mmol/L) (3.5–4.8 mmol/L)	2.8 ± 0.6	3.1 ± 1.0	3.3 ± 1.0	0.53
BUN (mg/dL) (15–32 mg/dL)	43 ± 21	56 ± 52	60 ± 20	0.47
Bicarbonate (mmol/L) (14–22 mmol/L)	18.5 ± 5.6	11.9 ± 3.3	15.3 ± 5.8	0.08
Osmolality (mOsm/kg) (290–310 mOsm/kg)	313 ± 17	318 ± 36	332 ± 27	0.30
pH (7.31–7.40)	7.326 ± 0.01	7.240 ± 0.11	7.243 ± 0.10	0.20

Data are presented as means ± standard deviation. Osmolality is a calculated value (see text). The blood bicarbonate concentration on presentation tended to be higher in Group 1 compared with Group 2, but this difference failed to reach statistical significance ($P = 0.03$). Group 1: cats prescribed a regular insulin CRI at 1.1 U/kg/day. Group 2: cats prescribed a regular insulin CRI at 2.2 U/kg/day. Group 3: cats initially prescribed a regular insulin CRI at doses starting at 1.1 U/kg/day, but which required greater insulin administration to address hyperglycemia.

each cat before the change in mentation ranged from 0.44 to 2.05 U/kg/d. Two of these cats (1 in Group 2 and 1 in Group 3) also had an osmolality > 350 mOsm/L at presentation. One was persistently hypotensive despite fluid and vasopressor therapy and was later euthanized. The other cat experienced a period of declining mentation status after receiving 12 hours of insulin CRI prescribed at 1.1 U/kg/d. No additional treatment was administered and the cat improved with time and survived to discharge. Two cats with presenting osmolality < 350 mOsm/L and declining mentation status were treated with mannitol for suspected cerebral edema. Both were in Group 3 and one had a seizure before receiving mannitol. The patient that had a seizure was prescribed 2.2 U/kg/d of insulin at the time the seizure occurred; the other of these 2 cats was prescribed 1.1 U/kg/d at the time that declining mentation status was noted in the medical record. Neither had a documented BG drop > 2.8 mmol/L/h (50 mg/dL/h). Both cats made a complete recovery and survived to discharge.

The insulin CRI was administered for 2.5 (0.8) days in Group 1, 3.6 (1.7) days in Group 2, and 4.6 (2.1) days in Group 3. Group 3 received the CRI for a longer time than Group 1 ($P = 0.02$).

During the first 24 hours of treatment with an insulin CRI, Group 1 cats were administered a mean dose of 0.34 (0.16) U/kg/d of regular insulin. This administered dose was significantly less than Group 2, which were administered a mean dose of 0.76 (0.26) U/kg/d of regular insulin ($P < 0.001$, Figure 1). Group 3 cats required increasing amounts of insulin over the 3-day period, and by 72 hours were being administered a mean dose of 0.87 (0.32) U/kg/d, a statistically significantly greater daily dose than they were administered during the first 24 hours, 0.53 (0.18) U/kg/d ($P < 0.0001$, Figure 1). No other statistically significant differences were identified between groups or among groups over the first 3 days during which they received IV insulin.

Once the insulin CRI commenced, Group 2 cats reached a BG ≤ 13.9 mmol/L (250 mg/dL) within a mean of 7.1 (6.0) hours, whereas Groups 1 and 3 cats reached a BG ≤ 13.9 mmol/L (250 mg/dL) in 13.4 (17.0) hours, and 15.1 (15.7) hours, respectively. Post hoc pairwise comparisons did not reveal any differences. There was no overall difference in average minimum BG per 4 hours over the first 36 hours of insulin CRI administration between the groups ($P = 0.75$, Figure 2). Additionally, there was no overall difference found in the change in BG from baseline per 4 hours between the groups over the first 36 hours of insulin CRI

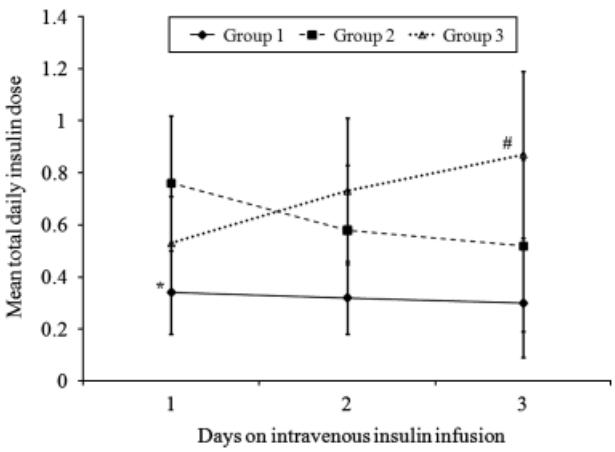

Figure 1: Mean total daily insulin dose (U/kg/d) administered to 3 groups of cats receiving intravenous insulin infusions for diabetic ketosis and diabetic ketoacidosis. Data points represent mean values and error bars represent standard deviation. *Significant difference from Group 2 mean value for the same day with a *P*-value = 0.0005. #significant difference from Group 3 mean value on Day 1 with a *P*-value of < 0.0001. Group 1: cats prescribed a regular insulin CRI at 1.1 U/kg/d. Group 2: cats prescribed a regular insulin CRI at 2.2 U/kg/d. Group 3: cats initially prescribed a regular insulin CRI at doses starting at 1.1 U/kg/d, but which required greater insulin administration to address hyperglycemia.

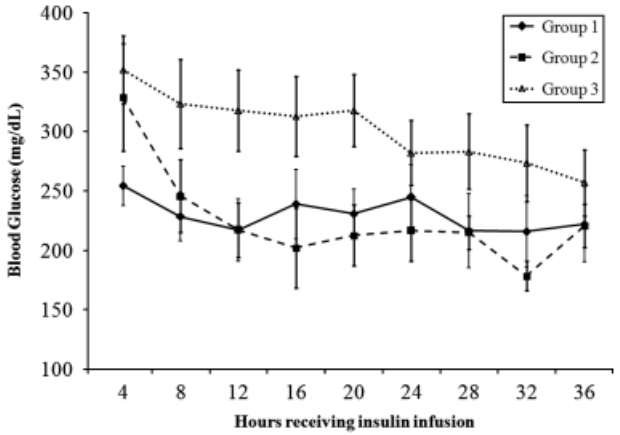

Figure 2: Mean minimum recorded blood glucose per 4 hours in Groups 1, 2, and 3. Data points represent the mean blood glucose in each group, error bars represent the standard error. Blood glucose was measured with a hand-held glucometer[c,d] or a blood chemistry analyzer[a,e] and was recorded every 4 hours after a constant rate of intravenous infusion of regular insulin was started. Group 1: cats prescribed a regular insulin CRI at 1.1 U/kg/d. Group 2: cats prescribed a regular insulin CRI at 2.2 U/kg/d. Group 3: cats initially prescribed a regular insulin CRI at doses starting at 1.1 U/kg/d, but which required greater insulin administration to address hyperglycemia.

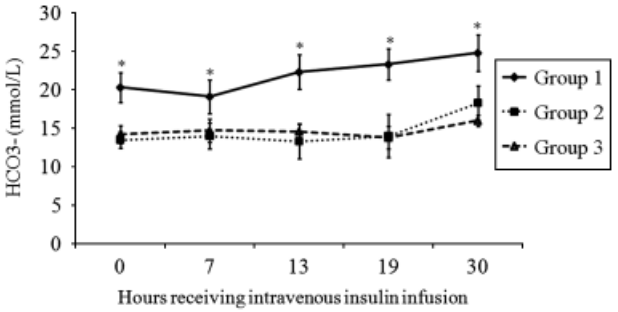

Figure 3: Serum bicarbonate concentration (HCO_3^-) in cats with diabetic ketosis/diabetic ketoacidosis treated with an insulin CRI over time. Data points represent the mean serum bicarbonate in each group, error bars represent the standard error. Group 1: cats prescribed a regular insulin CRI at 1.1 U/kg/d. Group 2: cats prescribed a regular insulin CRI at 2.2 U/kg/d. Group 3: cats initially prescribed a regular insulin CRI at doses starting at 1.1 U/kg/d, but which required greater insulin administration to address hyperglycemia. *Significant difference between Groups 2 and 3 ($P < 0.005$).

administration ($P = 0.77$). Furthermore, when analyzed separately for each individual time point, no differences were identified between the groups in regards to the change in BG from baseline per 4 hours over the first 36 hours of insulin CRI administration.

Blood bicarbonate concentration was evaluated after the insulin CRI commenced in 23 cats. When evaluated over time, Group 1 had significantly higher blood bicarbonate concentration than cats in Group 2 ($P = 0.003$), and Group 3 ($P = 0.0009$, Figure 3). No cats in Group 1 received any supplemental sodium bicarbonate, whereas 43% of cats in Group 2% and 50% of cats in Group 3 received multiple doses of sodium bicarbonate.[j]

Phosphorous was evaluated daily in 22 cats, and there were no significant differences in serum phosphorus relative to baseline between all 3 groups ($P = 0.53$). Serum potassium concentration was evaluated over a 40-hour period in 24 cats, and there were no significant differences in serum potassium concentration relative to baseline between all 3 groups ($P = 0.90$).

The median time cats in Group 2 became ketone negative was 49 hours (IQR: 35–84), whereas the median time cats in Groups 1 and 3 became ketone negative was 76 hours (IQR: 50–84 and 24–88, respectively, $P = 0.73$). The median time cats in Group 1 commenced eating was 16 hours (IQR: 6–21 h), compared with the median time cats in Groups 2 and 3 commenced eating was 60 (IQR: 8–91) hours and 65 (IQR: 24–85) hours ($P = 0.24$), respectively. The difference in length of hospitalization between the 3 groups was not different ($P = 0.63$). The mean length of hospitalization for cats in Group 1 was 6 (2.9) days, whereas the mean length of hospitalization for cats in Groups 2 and 3 was 7.1 (2.9) days, and 7.3 (3.2) days, respectively. Twenty-seven of the 29 cats (93%) survived to discharge. None of the cats died naturally, but 2 of the 29 cats were euthanized during their hospitalization, 1 from Group 2 and 1 from Group 3.

Post hoc analysis revealed that the 10 cats that received the greatest and the 10 cats that received the smallest amount of insulin [greatest, mean (SD): 0.8 (0.16) U/kg/d; smallest, mean (SD): 0.31 (0.09) U/kg/d] did receive significantly different mean doses of insulin per day ($P < 0.001$), and thus further analysis of these groups was undertaken. The length of hospitalization was not different between the 2 groups ($P = 0.732$). Further, neither the frequency of death or euthanasia nor the frequency of declining mentation status was found to be different between the 2 groups. Only 1 cat of the 20 included in this portion of the analysis died or was euthanized (in the greatest insulin received group). Likewise, only 1 cat of the 20 included in this portion of the analysis was reported to have declining mentation (also in the greatest insulin received group, but this was not the same cat that did not survive).

Discussion

This study did not demonstrate any significant differences in biochemical parameters, neurologic function,

and duration of care in 3 different treatment groups of cats with DK/DKA. These cats were assigned to groups that were analyzed based on the prescribed daily dose of insulin, one of which is the recommended cat dose published in veterinary textbooks and scientific literature (1.1 U/kg/d).[5,6,13] However, most cats did not actually receive the entire prescribed daily dose, similar to the findings reported in the canine insulin study by Macintire et al.[14] Although the goal of this study was to assess for differences in the aforementioned parameters between groups prescribed different daily doses of insulin that are based on widely accepted recommendations for canine or feline patients (and therefore the more clinically relevant question), analysis of cats grouped based on the actual doses received was performed in a post hoc manner as well. Analyzing the groups based on prescribed dosing regimens was initially chosen to better reflect how insulin infusions are actually used in veterinary practice wherein a desired maximal daily dose is prepared, but is rarely administered in its entirety due to adjustments in infusion rates in response to alterations in BG concentrations.

The signalment, history, and presence of previously diagnosed DM was similar between the groups, but cats in Group 1 appeared healthier than cats in Group 2 as evidenced by developing an appetite sooner, having an average normal blood pH, and higher blood bicarbonate concentrations and heart rates compared with cats in Group 2. In addition, more cats in Group 2 were hypothermic and underweight than cats in Group 1. Unfortunately, there are no validated illness severity scores for cats, but it is possible that the perceived severity of illness did affect the clinician's decision to treat more or less aggressively with insulin. Despite the differences between groups, the cats in both groups had similar recovery times and there were no clinically apparent adverse effects in cats prescribed the higher dose of insulin. Cats in Group 1 took more time to reach target BG and to become ketone negative than cats in Group 2. Although the difference in length of time to reach target BG or to test negative for ketones between Group 1 and Group 2 was not significant, there was a shorter range of time to reach target BG and to test negative for ketones when cats were prescribed the higher dose of insulin. Despite this, there was no difference in length of hospitalization.

In the present study, cats prescribed the higher dose of insulin did not have complications associated with hypoglycemia, hypophosphatemia, or hypokalemia. All cats were supplemented with potassium and dextrose, and many cats received phosphorous supplementation. Total magnesium and ionized magnesium were not assessed regularly in many cats in this study leading to incomplete data sets. However, regular monitoring of magnesium levels is important because ionized magnesium is commonly deficient in cats with DM and DKA, and total magnesium decreases significantly with insulin therapy in cats with DKA.[18] Magnesium deficiency has been associated with poor glycemic control, insulin resistance, and hypertension in humans with DM, but these pathologies were not found to be correlated with hypomagnesemia in a population of diabetic cats.[18,19,20] Whether hypomagnesemia contributes significantly to morbidity associated with DM or DKA in cats remains unknown.

Similar to cats with DKA described elsewhere, the majority of cats in this study were hyperosmolar at presentation.[6] A relationship was not found between presenting osmolality and declining mentation status in the cats of this study, regardless of prescribed insulin CRI dose or whether IV fluids were administered before initiating insulin CRI. It has been suggested that hyperosmolar DK/DKA cats are at risk for developing cerebral edema if prescribed 2.2 U/kg/d of a regular insulin CRI.[6] The hypothesized mechanism for the development of cerebral edema is as follows: neurons and glial cells produce organic osmoles, including taurine and inositol, during exposure to a hypertonic environment. This balances intracellular with extracellular osmolality and prevents cellular dehydration. When hyperglycemia is acutely corrected, the osmolality outside the cell changes more rapidly than the osmolality within the cell, since the aforementioned newly formed neuronal and glial organic osmole concentrations generally decline slowly. Subsequently, free water moves into the cell and cerebral edema results.

The development of cerebral edema in patients with DKA is likely related to factors other than a decrease in serum osmolality with insulin therapy. For the last 20 years, physicians have been using low doses of insulin and titrating to decrease BG by <2.8 mmol/L/h (50 mg/dL/h), and yet the incidence of cerebral edema has not changed.[21] There are several theories as to why cerebral edema occurs in some patients and not others, but no definitive cause has been elucidated. There is evidence that cerebral edema is present in DKA patients before receiving any treatment.[22] A recent study examining children with DKA showed that they have impaired cerebral blood flow autoregulation, such that the rate of cerebral blood flow is much higher than expected, leading to vasogenic cerebral edema.[23] Vasogenic edema occurs secondary to fluid expansion of the extracellular fluid compartment due to changes in Starling's forces. This is in contrast to cytotoxic edema, which involves cellular expansion from water moving into the cells due to osmotic gradients, the type traditionally thought to occur in DKA patients. Another study in children with DKA by Glaser et al[24] demon-

strated that vasogenic edema predominates and little cytotoxic edema was present. Increased cerebral blood flow coupled with damage to the microvasculature by ketone bodies (causing increased permeability and leak) was proposed by these authors to be the predominant mechanism by which cerebral edema occurs in DKA patients.[24]

There have been recent studies showing that BG does not correlate with serum osmolality in dogs and cats with DM and DK.[7,8] Effective osmolality in these patients was instead closely correlated with changes in serum sodium concentrations. These findings, coupled with the data collected in our study, suggest that it is not necessary to prescribe 1.1 U/kg/d as the insulin CRI dose in all cats with DKA. As there was no correlation between presenting osmolality and declining mentation status, regardless of dose of insulin prescribed, it is unlikely that the decline in mentation status seen in 4 of the cats in this study was due to rapid changes in blood osmolality. There are many other possible causes for neurological decline in these critically ill cats. In the present study, 96% of the population had concurrent clinical abnormalities including anemia, pancreatitis, and hepatic lipidosis. Subsequent cerebral hypoxemia due to severe anemia, severe systemic inflammatory response syndrome secondary to pancreatitis, and hepatic encephalopathy resulting from liver dysfunction can all lead to a progressive decline in mentation.

No differences between Groups 1 and 2 or Groups 2 and 3 were observed regarding total time insulin CRI was administered. Cats in Group 3 spent a longer period of time receiving an insulin CRI than did cats in Group 1. Both groups were initially prescribed 1.1 U/kg/d of the insulin CRI. Group 1 remained at this prescribed dose until the CRI was discontinued, whereas cats in Group 3 had their prescribed doses increased due to persistent hyperglycemia, ketonemia, and ketonuria. An insulin CRI was discontinued when a patient was eating and was no longer ketonemic or ketonuric. Group 1 cats trended toward eating sooner than cats in Group 3. It remains to be determined whether initially prescribing cats a higher dose of insulin will decrease the length of time an insulin CRI is required.

Interestingly, the actual administered doses of insulin were much lower than the prescribed doses, with cats in Groups 1 and 2 receiving between 24% and 35% of their prescribed doses. The hourly rate of administration of the insulin solution is based on every 2-hour BG assessments. In order to receive the full-prescribed dose, the infusion would need to be delivered at 10 mL/h for 24 hours. Instead, most cats received one-quarter to one-third this rate of administration (Figure 1). This finding suggests that it may be important to reassess the recommended doses of insulin published in the literature for the treatment of cats with DKA. An important next step will be to assess administration of predetermined doses of insulin in cats with DKA to establish which doses are most effective with the fewest side effects.

The present study examined a total of 29 cats with DK or DKA that were prescribed the published feline dose, the published canine dose, or a dose escalating beyond the published feline dose of regular insulin as an IV constant rate infusion.[5,6,13] The data from this study does not support the notion that prescribing 2.2 U/kg/d of regular insulin in cats (versus the widely utilized 1.1 U/kg/d) is more likely to lead to a rapid decrease in BG and free water shifts with subsequent cerebral edema, or transcellular electrolyte shifts with subsequent hypokalemia and hypophosphatemia.

While the main focus of this study was to compare outcomes in DKA cats that received insulin CRIs using either the recommended feline approach (1.1 U/kg/d) or the recommended canine approach (2.2 U/kg/d), a further post hoc analysis was performed in which the group assignments were based on actual insulin dose administered. By limiting the analysis to the 20 cats (10 in each group) that received the most widely disparate insulin doses, a statistically significant difference in the mean daily insulin dose received between the 2 groups was demonstrated. Analysis of these groups revealed that the frequency with which declining mentation or mortality was observed was not different between the groups. However, it must be noted that declining mentation and mortality are rare events (5% for each among the 20 cats in the post hoc analysis) and the present study is insufficiently powered to detect a true 5% difference in the frequency of these events. A post hoc analysis revealed that 201 cats would need to have been included in the study to achieve sufficient statistical power to discern a true difference of this size between the groups. To achieve this sample size the retrospective analysis would have had to include cats from a much longer time period (several decades) or enrolled patients from other institutions introducing additional confounding variables.

It is of interest that 3 of the 4 cats in which declining mentation status was noted belonged to the group of 9 cats that received intermediate mean daily insulin doses (and were excluded from the post hoc analysis). In addition 1 of the 2 cats that did not survive was also in this group of 9 cats. This suggests that neither mortality nor declining mentation is an outcome that is very tightly linked to daily dose of insulin received in feline DKA patients. These findings underscore the need for a larger prospective study of insulin CRI dos-

ing protocols in feline patients to determine optimal daily dosage and rate of administration.

There are several limitations that must be recognized when interpreting the findings of this study. The major limitation is that this is a retrospective study of a small patient population. There was no predetermined protocol for the administration of the insulin CRI based on measured BG. Since some portable glucometers can underestimate BG, it would have ideally been measured using the same machine for all time points, but this was not the case. The BG was measured on any of 3 devices, and measurements were not always obtained at exactly 2-hour intervals. The phosphorous and potassium changes were not compared between cats over time because there was no set protocol for measurement or supplementation of these electrolytes. It is possible that some cats became ketone negative in between actual measurements of ketones since the frequency of monitoring was not uniform. Additionally, many cats only had urine ketones recorded, while others only had serum ketones recorded. Urine ketones may be present for a longer period of time because urine comprises a pooled sample of the previous several hours of filtered plasma. Finally, there is a possibility that the cats in this study produced primarily B-hydroxybutyrate ketones, which would not have been assessed by the colorimetric strip, and thus would have falsely tested ketone negative.

For most parameters examined in this study, the population in each group was too small to display any significant differences between the groups. For example, a sample size of at least 17 in each group ($n = 51$ total) would have been required to show a difference equivalent to 1 SD in a given parameter. However, this information does suggest that the canine protocol (2.2 U/kg/d) for a regular insulin CRI in cats with DK or DKA is not associated with clinically apparent detrimental effects. Additionally, the total prescribed insulin dose is rarely actually administered as explained above. Future studies prospectively evaluating the optimal hourly/daily dose of insulin when given as a CRI for cats with DK or DKA are warranted.

Footnotes

[a] NOVA, Biomedical Corporation, Waltham, MA.
[b] Keto-Diastix Reagent Strips, Bayer Corporation, Leverkusen, Germany.
[c] Accu-chek Advantage, Roche, Mannheim, Germany.
[d] iStat, Heska Company, Waukesha, WI.
[e] Ortho 250 Chemistry analyzer, Ortho-Clinical Diagnostics, Rochester, NY.
[f] Humulin R, Eli Lilly and Company, Indianapolis, IN.
[g] Microsoft Excel for Windows XP, Redmond, WA.
[h] SAS statistical software, Version 9.1, SAS Institute, Cary, NC.
[i] Sigmaplot 11, Systat Software Inc., San Jose, CA.
[j] 8.4% sodium bicarbonate, Neogen Vet, Lexington, KY.

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