CHAPTER 115   Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

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Dogs and cats afflicted with either diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS) can become acutely ill and benefit from prompt diagnosis and treatment. These disorders usually occur in middle-aged to old pets, often after a variable period of time characterized by polydipsia, polyuria, and weight loss. Alternatively, they can occur as acute metabolic complications of other conditions, such as acute pancreatitis or sepsis. The primary pathophysiology, clinical signs, and medical management of these interesting and challenging disorders are discussed in this chapter. Certain clinical findings shared by the two syndromes are discussed in the section on ketoacidosis.

PATHOPHYSIOLOGY OF KETOACIDOSIS

Hyperglycemia and accelerated ketogenesis occur when there is an absolute or relative deficiency of insulin and a relative excess of glucagon and other "counter regulatory hormones" such as cortisol, growth hormone, and epinephrine. Consequently, glucose and ketoacids are both overproduced and underutilized. Because the pathophysiologic details of DKA are discussed elsewhere in this text and throughout the medical literature, only those germane to the care of the critically ill patient are mentioned in this section.

The nitroprusside reaction is used to detect and semiquantitate plasma, serum, and urinary ketones. The test detects acetone and acetoacetate but does not react with beta hydroxybutyrate. This characteristic has clinical importance in situations in which shocklike states promote the production of beta hydroxybutyrate, thereby disabling clinical detection of ketoacidosis with the nitroprusside test.

After institution of insulin treatment, the beta hydroxybutyrate to acetoacetate (B:A) ratio decreases as a result of the metabolism of beta hydroxybutyrate to acetoacetate. Although acetoacetate concentrations eventually decrease, the shifting B:A ratio explains the clinical paradox occasionally encountered in which test results initially are negative for ketones but, with the same test given on the second and third days of treatment, are positive despite clinical improvement. A lingering ketonuria can also occur as a dog or cat improves because of the delayed clearance of acetone. Therefore it is not uncommon for ketones to persist well into the third or fourth hospital day while the pet shows signs of improvement.

DIAGNOSIS

History and Physical Examination

The history for either DKA or HHS often indicates that anorexia, depression, weakness, and vomiting have been observed for only 1 to 3 days. A complete physical examination is essential to detect any concurrent disorders that can significantly affect the outcome. It has been suggested that both conditions are invariably associated with concurrent disorders. The term *diabetic coma* is frequently used to describe the mental effects of the ketoacidotic and hyperosmolar conditions, but only a small percentage of dogs or cats actually have profound decreases in consciousness.

DIAGNOSTIC EVALUATION

Medical evaluation of a sick diabetic dog or cat should be thorough and should include thoracic radiographs, abdominal ultrasound scans, hematology, serum chemistry, and urinalysis. The acquired information creates an important data base for subsequent medical and sometimes surgical management.

Because hepatic production of glucose is increased in diabetic dogs or cats, the degree of hyperglycemia is determined by the severity of plasma volume depletion. Therefore extreme levels of hyperglycemia tend to occur only when extracellular fluid volume and blood pressure have decreased so much that urine flow is impaired. This is most obvious in dogs or cats that have extreme increases in blood glucose concentrations with minimal glucosuria. Marked hyperglycemia may also signify oliguria.

Metabolic acidosis is mainly attributed to ketoacid buildup, but acidosis can be enhanced by coexisting disease, such as renal failure and lactic acid production. The metabolic acidosis often is accompanied by a large anion gap (AG) (greater than 30 mEq/L) that can be calculated using the following formula:

$$AG = (Na^+ + K) - (HCO_3^- + Cl^-)$$

Hyponatremia in both syndromes can be factitious (attributable to hypertriglyceridemia) or real (due to urinary or gastrointestinal loss of sodium ions). Spurious hyponatremia can also occur when increases in the plasma glucose concentration draw water into the extracellular space, thereby diluting plasma constituents.

The serum potassium concentration in DKA and HHS can range from low to normal to increased. Hyperkalemia can result from a shift of potassium from the intracellular to the extracellular space as a consequence of acidemia, insulin deficiency, and plasma hyperosmolarity. It may also be associated with oliguric or anuric acute renal failure.

Hypokalemia is the most common and most serious electrolyte disturbance. This is usually a reflection of a substantial reduction in total body potassium stores. Even patients with normokalemia may have a considerable deficit of total body potassium; because 98% of total body potassium is intracellular, these concentrations are not easily assessed. Potassium losses occur with vomiting and osmotic diuresis and can be further complicated by therapy. Serum dilution from rehydration, continued urinary losses, correction of acidosis, and increased cellular uptake can "unmask" hypokalemia.

Phosphorus is an integral component of lean body mass. The enhanced catabolism of muscle and fat that invariably occurs in diabetes mellitus results in increased urinary phosphorus excretion and phosphorus wasting.

Increased serum liver transaminase (ALT) and alkaline phosphatase (SAP) activity is commonly attributable to the hepatic lipidosis that occurs in patients with DKA. Hypovolemia-induced central lobular necrosis can also increase liver enzyme values. These hepatic changes are completely reversible, and serum liver enzyme activity moves toward normal after successful treatment. Because diabetic dogs and cats almost always have abnormal liver enzyme values, it is not common for these test results to completely "normalize."

Azotemia can be either prerenal or renal in origin. Extensive primary renal dysfunction is characterized by isosthenuria (fixed urine specific gravity of 1.008 to 1.012) in a dehydrated patient and an accompanying azotemia that does not readily resolve with rehydration. It should be remembered, however, that both glycosuria and hyperosmolarity can raise a urine specific gravity that remains "isosthenuric" (a specific gravity of 1.020 when the serum osmolality is 400 does not indicate good renal function). Urine sediment should be screened for any signs of infection such as pyuria and bacteriuria. Urine output should be monitored to detect oliguria or anuria.

A leukocytosis with a mature neutrophilia in the 20×10^3 range can be due to the stress associated with both disorders. Detection of bands and toxic cell changes should prompt a search for an inflammatory focus, which may or may not be accompanied by an infection.

TREATMENT

Fluid and Electrolytes

Disturbances in hydration and electrolyte balance are of great importance in DKA and HHS and require expedient correction (Figure 115-1). The calculated fluid requirements include the patient's dehydration deficits, the 24-hour maintenance needs, and extra losses that

result from vomiting or diarrhea. The dehydration status is approximated on a scale ranging from mild (5%) to extreme (12%). The needed isotonic crystalloid fluid replacement volume can be calculated using either of the following equations:
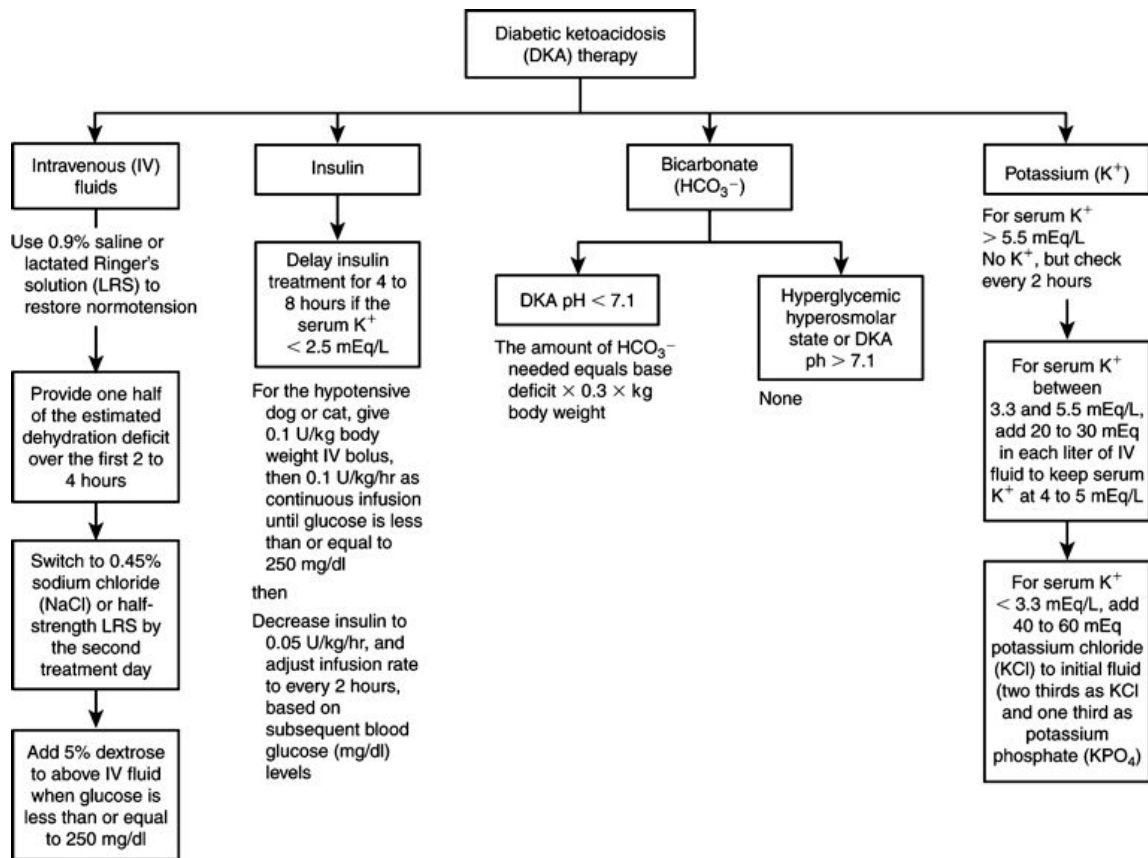
- Dehydration volume deficit (mL) = Dehydration (%) × Body weight (kg) × 1000

- Dehydration (%) × Body weight (lb) × 500

The 24-hour maintenance volume is roughly estimated (assuming adequate urine output) at 66 mL/kg (30 mL/lb). Therefore the first 24-hour total fluid volume is the sum of the dehydration and the maintenance volumes plus any ongoing losses from vomiting or diarrhea.

If the animal is 8% to 12% dehydrated, half of the estimated dehydration deficit should be administered intravenously over the first 2 to 4 hours of hospitalization; the remaining replacement and maintenance volumes, given over the following 20 to 22 hours, should be accompanied by any adjustments necessitated by changes in urine volume.

Hydration alone can substantially decrease the blood glucose level and hyperosmolarity. Hypovolemia in DKA and HHS is corrected with isotonic solutions, such as lactated Ringer's solution or 0.9% saline. Recommended maintenance solutions include 0.45% saline or half-strength lactated Ringer's solution. Dextrose solutions (2.5% to 5%) are used when the patient's blood glucose declines to 250 mg/dL or less in the setting of continued insulin administration.

Figure 115-1   Algorithm for the management of the critically ill dog and cat with diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome. (Modified from Umpierrez GE et al: Hyperglycemic crises in urban blacks. Arch Intern Med 157:669, 1997.)

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                        ┌─────────────────────────┐
                        │  Diabetic ketoacidosis  │
                        │      (DKA) therapy      │
                        └─────────────────────────┘
         ┌────────────────┬─────────────────────┬──────────────────┐
         ▼                ▼                     ▼                  ▼
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│Intravenous(IV)│  │   Insulin    │   │   Bicarbonate    │  │ Potassium(K⁺)│
│    fluids     │  │              │   │    (HCO₃⁻)       │  │              │
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$Bicarbonate\ (HCO_3^-)$ / $Potassium\ (K^+)$

Intravenous (IV) fluids

Use 0.9% saline or lactated Ringer's solution (LRS) to restore normotension

↓

Provide one half of the estimated dehydration deficit over the first 2 to 4 hours

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Switch to 0.45% sodium chloride (NaCl) or half-strength LRS by the second treatment day

↓

Add 5% dextrose to above IV fluid when glucose is less than or equal to 250 mg/dl

Insulin

Delay insulin treatment for 4 to 8 hours if the serum K^+ < 2.5 mEq/L

For the hypotensive dog or cat, give 0.1 U/kg body weight IV bolus, then 0.1 U/kg/hr as continuous infusion until glucose is less than or equal to 250 mg/dl

then

Decrease insulin to 0.05 U/kg/hr, and adjust infusion rate to every 2 hours, based on subsequent blood glucose (mg/dl) levels

Bicarbonate (HCO_3^-)

- DKA pH < 7.1 → The amount of HCO_3^- needed equals base deficit × 0.3 × kg body weight
- Hyperglycemic hyperosmolar state or DKA ph > 7.1 → None

Potassium (K^+)

For serum K^+ > 5.5 mEq/L No K^+, but check every 2 hours

↓

For serum K^+ between 3.3 and 5.5 mEq/L, add 20 to 30 mEq in each liter of IV fluid to keep serum K^+ at 4 to 5 mEq/L

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For serum K^+ < 3.3 mEq/L, add 40 to 60 mEq potassium chloride (KCl) to initial fluid (two thirds as KCl and one third as potassium phosphate (KPO_4))

Hyponatremia for both disorders is corrected with intravenous 0.9% saline solution to avoid any plasma hypo-osmolality that might occur when the hyperglycemia is reduced with insulin treatment. Plasma hypo-osmolality can cause a reversal of osmotic gradients and overexpansion of the intracellular compartment with resultant cerebral edema.

Potassium supplementation is best provided by adding potassium chloride solution to the parenteral fluids. If concurrent hypophosphatemia is present, one third of the potassium supplement can be in the form of potassium phosphate. Potassium supplementation is best begun after the first 2-hour period of fluid replacement, when hydration, blood pressure, and urine output are improved. If the patient is initially hypokalemic, potassium chloride (KCl) can be added to the hydrating solution; however, the infusion should be slowed so that half the dehydration replacement volume is delivered over an additional 1 to 3 hours. Although most texts list the maximum rate of potassium ion administration as 0.5 mEq per kilogram of body weight (BW) per hour, the author's experience has shown that this rate can be safely doubled when the patient is severely hypokalemic (serum potassium level less than 2.5 mEq/L) as long as electrocardiographic and urine output monitoring is done. The recommended amount of potassium that can be added to the parenteral fluids *over a 24-hour period* is shown, using two different but equally effective methods.

- *Mild hypokalemia* (serum K^+ of 3.0 to 3.5 mEq/L): administer 2 to 3 mEq/kg *or* add 20 to 30 mEq KCl per liter of replacement fluid

- *Moderate hypokalemia* (serum K^+ of 2.5 to 3.0 mEq/L): administer 3 to 5 mEq KCl/kg *or* add 40 to 60 mEq KCl per liter of replacement fluid

- *Severe hypokalemia* (serum K^+ below 2.5 mEq/L): administer 5 to 10 mEq KCl/kg *or* add 60 to 80 mEq KCl per liter of replacement fluid.

Daily serum electrolyte determinations and the necessary treatment adjustments are made until normal values are obtained. Intravenous fluids are discontinued when serum biochemistry values are normal, hydration is normal, and the patient is able to eat and drink without vomiting.

Any needed phosphate replacement can be given as potassium phosphate solution at the recommended dose of 0.01 to 0.03 mmol/kg BW/hour, with repeat serum phosphorus determinations every 6 hours. Attention should be given to avoiding iatrogenic hyperphosphatemia and hypocalcemia.

Hypomagnesemia has been shown to cause specific problems, especially cardiac arrhythmias, in diabetic humans; however, its association with any particular dysfunction in diabetic dogs and cats has not yet been demonstrated. The ionic and total bound forms of magnesium can be measured.

Sodium bicarbonate treatment for DKA is controversial. Advocates of this treatment cite concern that severe acidosis (blood pH less than 7.0) can adversely affect cardiovascular function; opponents base their concern on the treatment's causal relationship with paradoxical cerebrospinal fluid acidosis, hypokalemia, and worsened intracellular acidosis with overshoot alkalosis.

The use of sodium bicarbonate should be restricted to dogs or cats with a blood pH below 7.1 or those with a serum total carbon dioxide (CO_2) concentration less than 10 to 12 mEq/L. During most treatment courses, metabolic acidosis reverses without bicarbonate treatment because of the cessation of ketogenesis, the metabolic conversion of ketones to bicarbonate after initiation of insulin treatment, improved renal function, and conversion of the lactate in lactated Ringer's solution to bicarbonate. In severe cases of metabolic acidosis (i.e., an anion gap greater than 30 mEq/L and an arterial pH less than 7.1), sodium bicarbonate ($NaHCO_3$) can be given according to the following equation:

$$NaHCO_3 \text{ (mEq)} = \text{Base deficit (mEq)} \times 0.3 \times \text{Body weight (kg)}$$

Subsequent alkali treatment depends on the results of repeat plasma pH measurements; it should be discontinued when the blood pH has been restored to 7.2 or higher or until the serum total CO_2 concentration is greater than 10 to 12 mEq/L.

Insulin

The cornerstone of management of a sick DKA or HHS dog or cat is insulin administration. Regular crystalline insulin is used when the pet has signs of depression, dehydration, anorexia, and vomiting. Regular insulin has several advantages, including its various routes of administration (intravenous, intramuscular, and subcutaneous), rapid onset of action, and short duration of action. These properties allow adequate insulin titration throughout the day according to the animal's needs. The clinician must remember that the blood glucose concentration declines much earlier than ketones, allowing for the persistence of ketonuria for the first 48 to 96 hours.

Regular insulin given intravenously by slow constant-rate infusion (CRI) is the preferred method of treatment for the critically ill hypotensive pet. The pet's hypovolemia should be partially corrected over the first 2 hours, before the insulin is administered.

A separate intravenous cannula is usually necessary for the insulin infusion. The CRI insulin solution is prepared by adding 5 U of regular insulin to a 500 mL bottle of 0.9% saline or lactated Ringer's solution to make up a solution that provides 0.01 U of insulin per milliliter. The infusion is delivered by an automatic injection syringe, an intravenous infusion pump, or a pediatric intravenous infusion set to deliver a therapeutic insulin dose of 0.1 U/kg BW/hour. To prevent binding of insulin to the intravenous lines, some clinicians prefer to run some of the diluted insulin infusion through the line before attaching it to the patient. Before this slow infusion is begun, the patient can receive an initial intravenous insulin bolus at a dosage of 0.1 U/kg. To avoid any complicating osmotic disequilibrium effects on the brain, the rate of decline in the blood glucose level should not exceed 75 to 100 mg/dL/hour. When the blood glucose level has declined to 250 mg/dL, after several hours of the CRI insulin infusion, the rate should be decreased to half the initial amount (i.e., 0.05 U/kg/hour), and dextrose should be added to the intravenous fluid to achieve a 2.5% to 5% dextrose concentration. The blood glucose level subsequently should be determined every 2 hours, using glucose oxidase reagent strips or a reflectance meter. Thereafter the rate of insulin infusion should be adjusted to maintain a blood glucose range of 150 to 250 mg/dL to avert hypoglycemia.

The disadvantages of the CRI insulin administration technique are the frequent need for a separate intravenous cannula, intensive care monitoring, and frequent monitoring of the blood glucose and serum potassium concentrations. If the patient initially is hypokalemic,

the clinician can begin treatment with isotonic fluids containing added potassium chloride and delay insulin treatment for the first 4 to 8 hours.

Low doses of regular insulin also can be given intramuscularly. Initially, 2 U are injected into the thigh muscles of cats and dogs weighing less than 10 kg. For dogs weighing more than 10 kg, the initial dose is 0.25 U/kg BW. Subsequent hourly injections of 1 U for cats and small dogs and 0.1 U/kg BW for larger dogs are given until the blood glucose level is less than 250 mg/dL, at which time the subcutaneous route can be used to administer the insulin every 6 hours or as needed. The low doses used in this technique can be accurately measured with a special low-dose calibrated syringe.

Subcutaneous administration of regular insulin is a suitable alternative to the intravenous and intramuscular methods when intensive care monitoring is unavailable and when the patient is alert and normotensive. The initial dose is 0.5 U/kg BW, with subsequent doses given every 6 to 10 hours, depending on the need.

The patient is regarded as stable when normal hydration has been restored, blood glucose levels are below 250 mg/dL, serum and urine ketones are minimal to absent, and eating resumes. Subsequent insulin treatment can be changed to the intermediate-acting or the ultra-long-acting type.

COMPLICATIONS

The main complications of insulin treatment include hypo-glycemia, hypokalemia, cerebral edema, metabolic alkalosis, and paradoxical cerebrospinal fluid acidosis. Most of these problems are avoidable with meticulous medical management geared toward avoiding overtreatment of the patient.

HYPERGLYCEMIC HYPEROSMOLAR SYNDROME

The hyperglycemic hyperosmolar syndrome (HHS) is characterized by extreme dehydration, renal dysfunction, abnormal brain function, marked hyperglycemia, and the lack of significant ketoacidosis. The incidence of this disorder in the dog and cat has not been reported; however, isolated case reports can be found in the veterinary literature spanning the past 25 to 30 years. Underlying renal disease and a precipitating condition, such as an infection or pancreatitis, can often be found.

PATHOPHYSIOLOGY

Only the main pathophysiologic mechanisms are covered in this section. The development of HHS is attributed to three main factors: (1) decreased insulin utilization and glucose transport, (2) increased hepatic gluconeogenesis and glycogenolysis, and (3) impaired renal excretion of glucose.

Two concepts have been advanced to reasonably explain the pathophysiology of HHS. The first suggests that an insulinized liver (reflecting residual beta cell secretory activity) coexists with a diabetic periphery, resulting in inactivation of intrahepatic oxidation of incoming free fatty acids, which are directed largely along nonketogenic metabolic pathways, such as triglyceride synthesis. This could account for the absence of hyperketonemia. The second proposal suggests that enhanced gluconeogenesis occurs in the liver due to the prevailing elevated portal vein ratio of glucagon to insulin. This effect, accompanied by severe dehydration (greater than 8%), is mainly responsible for the development of marked hyperglycemia.

The decrease in consciousness and the onset of the associated neurologic abnormalities that characterize HHS result from the direct effects of hyperosmolarity-induced dehydration on the brain parenchyma.

DIAGNOSTIC EVALUATION

Several clinicopathologic abnormalities characterize the HHS. The blood glucose levels are often elevated above 800 mg/dL. Serum osmolality is elevated (normal serum osmolality is 290 to 310 mOsm/kg body water) and can be determined by the freezing point depression method with an osmometer, or it can be calculated using the following formula:

$$sOsm = 2\left(Na^+ + K^+\right) + \frac{Glu}{18} + \frac{BUN}{2.8}$$

where Na^+ is serum sodium, K^+ is serum potassium, Glu is serum glucose, and BUN is blood urea nitrogen.

Most patients are azotemic, a condition that may be renal or prerenal in origin. The disturbances in serum electrolyte concentrations were described in the DKA section, above. It should be noted that an elevated serum sodium level during severe hyperglycemia can be explained only by significant plasma volume contraction caused by large water losses associated with hypotonic urine excretion.

TREATMENT

The main treatment objectives with HHS include reestablishment of normal hydration and adequate urine output; judicious use of insulin to avoid a precipitous decline in blood glucose levels; and ample potassium supplementation to make up the total body potassium deficit. Treatment techniques were described in the previous section. The regular insulin dosage requirements for the hyperglycemic hyperosmolar diabetic are oftentimes less than those needed to treat diabetic ketoacidosis, but the technique for delivery is the same.

The diabetic ketoacidotic and hyperglycemic hyperosmolar syndromes pose noteworthy challenges to the practicing clinician. A sound understanding of the underlying pathophysiology, along with logical and timely therapeutic intervention, can usually lead to a remarkably optimistic outcome.

(Ettinger, Stephen J.. *Textbook of Veterinary Internal Medicine: 2-Volume Set with, 6th Edition*. Saunders Book Company, 122004. 115).
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