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Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the culmination of diabetes mellitus that results in unrestrained ketone body formation in the liver, metabolic acidosis, severe dehydration, shock and possibly death. Hepatic lipid metabolism becomes deranged with insulin deficiency and non-esterified fatty acids are converted to acetyl-co-enzyme A (acetyl-CoA) rather than being incorporated into triglycerides. Acetyl- CoA accumulates in the liver and is converted into acetoacetyl-CoA and then ultimately to ketones including acetoacetic acid, beta-hydroxybutyrate (primary ketone in dogs and cats) and acetone. As insulin deficiency culminates in DKA, accumulation of ketones and lactic acid in the blood and loss of electrolytes and water in the urine results in profound dehydration, hypovolemia, metabolic acidosis and shock. Ketonuria and osmotic diuresis caused by glycosuria causes sodium and potassium loss in the urine exacerbating hypovolemia and dehydration. Nausea, anorexia and vomiting, caused by stimulation of the chemoreceptor trigger zone via ketonemia and hyperglycemia, contribute to the dehydration caused by osmotic diuresis. Dehydration leads to further accumulation of glucose and ketones in the blood. Stress hormones such as cortisol and epinephrine contribute to the hyperglycemia in a vicious cycle. Eventually severe dehydration may result in hyperviscosity, thromboembolism, severe metabolic acidosis, renal failure, and finally death.

Hyperosmolar non-ketotic diabetic mellitus (HONKDM) is a less common complication of DM. It has a similar pathogenesis to DKA with a relative deficiency in insulin. For the hyperosmolar syndrome to develop, some functioning beta cells must still be producing insulin. The existence of some insulin prevents the formation of ketones. Excessive dehydration leads to a decrease in GFR decrease in glucose excretion. Hyperglycemia worsens and causes an increase in plasma osmolality. Increased plasma osmolality draws water out of cerebral neurons resulting in obtundation, decreased water intake which ends in a vicious cycle.

HISTORICAL FINDINGS

Most dogs and cats with DKA present with a previous history of uncomplicated diabetes including polyuria and polydipsia and dramatic and rapid weight loss in the face of a good or even ravenous appetite. Additional more recent historical findings include anorexia, weakness, depression, vomiting and diarrhea. Occasionally owners fail to notice the significance of the classical signs of diabetes mellitus and the animals are presented solely with an acute history of DKA. It is also possible for DKA to develop in previously well-controlled treated diabetic patients. Patients with HONKDM typically are quite depressed. They may be comatose upon presentation. The history of weakness may be for several weeks prior to presentation.

PHYSICAL EXAMINATION FINDINGS

The most common physical examination findings in DKA are lethargy and depression, dehydration, unkempt haircoat, and muscle wasting. Hepatomegaly is common in both diabetic cats and dogs. Cataracts are commonly observed in diabetic dogs. A plantigrade rear limb stance resulting from diabetic neuropathy, is often observed in diabetic cats. Other findings include tachypnea, dehydration, weakness, vomiting, and occasionally, a strong acetone odor on the breath. Cats can present recumbent or comatose and this may be a manifestation of mixed ketotic hyperosmolar syndrome. Icterus can develop as a result of the complicating factors of hemolysis, hepatic lipidosis or acute pancreatitis.

LABORATORY FINDINGS

The average blood glucose in patients with DKA is 450 mg/dl. Values can range from 180 to > 900 mg/dl but the latter is more characteristic of hyperosmolar coma. Although portable glucose meters are commonly used and very accurate in both dogs and cats (Alpha-Trak; Zoetis) to monitor glucose concentrations in DKA, caution is advised in relying on these monitors for baseline glucose concentrations because of inaccuracies in the face of severe hyperglycemia (> 700 mg/dl). All DKA patients have a relative or absolute deficiency of insulin and excessive hepatic production of glucose resulting in hyperglycemia. Hyperglycemia is further exacerbated by dehydration and the corresponding reduction in glomerular filtration rate (GFR) and these factors are important determinants of its severity. This is supported by the findings that glucose concentrations exceed 450 mg/dl only when dehydration is severe enough to reduce GFR and thus the ability of the kidneys to excrete glucose, and that fluid administration alone can significantly reduce blood glucose concentrations.

Osmolality is usually mildly to markedly increased in the DKA patient as a result of hyperglycemia, but may not be detected, in part because of concurrent hyponatremia. Sodium and to a lesser extent, potassium, glucose, and urea concentrations are the determinants of the calculated serum osmolality. Reference values for serum osmolality in dogs and cats are approximately 290 to 310 mOsm/kg. Hyperosmolality is generally mild enough to resolve with intravenous fluid and insulin therapies.

Non-ketotic hyperosmolar diabetes is defined by extreme hyperglycemia (> 600 mg/dl), hyperosmolality (> 350 mOsm/L), severe dehydration, central nervous system (CNS) depression, no ketone body formation and absent or mild metabolic acidosis. Affected patients are more likely to have underlying renal or cardiovascular disease and are more likely to be non-insulin-dependent. Although this specific syndrome, as defined in humans, is uncommonly encountered in veterinary medicine, it is not uncommon to have ketotic or non-ketotic diabetic cats with significant hyperosmolality and CNS alterations.

Most patients suffering from DKA have a total body potassium deficit due to urinary (osmotic diuresis), anorexia and gastrointestinal (vomiting and anorexia) losses. The metabolic acidosis, relative or absolute insulin deficiency, and serum hypertonicity combine to cause a shift of potassium from the intracellular to the extracellular compartment. This is capable of masking the severity of total body hypokalemia when plasma concentrations are measured. Insulin therapy, as well as correction of the acid-base disturbance with fluids and/or bicarbonate will drive serum potassium intracellularly, potentially causing marked circulating hypokalemia. Polyuric patients are predisposed to severe hypokalemia, while oliguric or anuric patients are predisposed to severe hyperkalemia.

In general, DKA causes significant total body sodium deficits. Excessive urinary loss of sodium results from the osmotic diuresis induced by high glucose and ketone concentrations and the lack of insulin, which usually aids in reabsorption of sodium from the distal nephron. Hyperglucagonemia, vomiting, and diarrhea also contribute to the total body sodium loss. Hyperosmolality may contribute to a low sodium concentration because as osmolality increases, water is drawn from the interstitium into the vascular space, thus diluting plasma sodium and chloride.

Phosphorus is the major intracellular anion and is important for energy production and for maintenance of cell membranes. Concentrations are regulated by dietary intake, renal elimination, factors promoting its movement into and out of cells, and vitamin D and parathyroid interactions. In DKA, circulating concentrations are usually within reference range or increased initially because of dehydration and/or renal disease. Phosphorus may also be low at presentation because of urinary loss due to osmotic diuresis. As long as renal function is not

compromised, a significant decrease in phosphorus should be anticipated with therapy. Following insulin administration, phosphorus shifts to the intracellular compartment with glucose. Clinical signs of hypophosphatemia such as hemolytic anemia (also seen with Heinz bodies in DKA), lethargy, depression, and diarrhea may develop once concentrations reach 0.32 mmol/L. Over supplementation of phosphorus should be avoided as hypocalcaemia or metastatic calcification may result.

Magnesium (total serum) is not usually measured routinely, but concentrations may be abnormal in DKA. A recent study in cats demonstrated high total serum magnesium concentrations at presentation in patients with DKA, however after 48 hours of therapy, total serum magnesium concentrations were significantly decreased. Magnesium deficiency may be caused by poor oral intake, decreased intestinal absorption, increased renal loss, or changes in distribution as it is the second most abundant intracellular cation (Hansen 2000). Clinical signs of hypomagnesaemia include neuromuscular weakness and cardiac arrhythmias, signs that can be seen with other electrolyte alterations. Hypomagnesaemia can also cause decreases in other electrolytes such as potassium and calcium. Correction of deficits may resolve electrolyte disturbances and may improve clinical outcome in the severely deficient patient.

Liver enzyme elevations are common in diabetes mellitus. Further increases potentially occur in DKA. Alanine aminotransferase and aspartate aminotransferase are most commonly affected and these increase secondary to hypovolemia and poor hepatic blood flow, and subsequent hepatocellular damage. Further increases in serum alkaline phosphatase concentration may occur if pancreatitis and secondary cholestasis ensues. Cholesterol and triglycerides may be elevated secondary to derangements of lipid metabolism due to decreased insulin.

Metabolic acidosis is one of the most prominent features of DKA. As ketone bodies accumulate in the blood and overwhelm the body's buffering capabilities, there is an increase in hydrogen ions and a decrease in bicarbonate. As dehydration worsens, blood flow to peripheral tissues decreases and the resulting lactic acidosis may contribute to the acid-base derangement. Acidosis can be manifested as lethargy, vomiting, hyperventilation, decreased myocardial contractility, peripheral vasodilation, stupor, and coma. Initiation of insulin therapy to stop ketogenesis and fluid therapy to correct dehydration will help improve the metabolic acidosis in most patients. Bicarbonate supplementation should be pursued with caution and is generally not recommended unless the patient's blood pH is less than 7.1 or the serum bicarbonate is less than 12 mmol/L.

In DKA, ketones become unmeasured anions as they dissociate from ketoacids. However, if significant dehydration is present secondary to the osmotic diuresis and vomiting, lactic acidosis secondary to tissue hypoxia may contribute to the unmeasured anions, thus increasing the anion gap. Anion gap may be normal or elevated. An elevated value further characterizes the metabolic acidosis caused by DKA. The anion gap is a representation of the circulating anions not routinely measured on biochemical analyses. The normal anion gap ranges from 10 to 20 and is calculated by the following equation:

Osmolality (mOsm) = 2(Na + K mEq/L) + (glucose/18) + (BUN/2.8)

Circulating urea and creatinine concentrations may be within reference range or high. These values are high in most patients as a reflection of severe dehydration, but renal insufficiency or failure is also a possible cause for the elevation. Elevations of urea and creatinine must be evaluated in light of the urine specific gravity. A low urine specific gravity at presentation does not always guarantee a diagnosis of renal insufficiency or failure, as osmotic diuresis and chronic hypokalemia can contribute to low specific gravities in diabetic patients. Therefore, reevaluation of urea, creatinine, and urine specific gravity must be done after treatment of the crisis. If urea and creatinine are initially elevated and remain static or increase with appropriate therapy, concurrent renal disease is strongly suspected.

The most important part of urinalysis is measurement of glucose and ketones. A strongly positive glucose confirms diabetes mellitus and a positive result for ketones confirms DKA. However, a negative ketone result does not definitively rule out ketosis. The nitroprusside reagent used in urine sticks detects only acetoacetate and acetone. It is not as sensitive for beta-hydroxybutyrate, the most prevalent ketone body, and therefore, may be negative in the face of ketosis. A recent study reported that beta-hydroxybutyrate concentrations above 1.9 mmol/L were the most sensitive indicator of DKA and that values above 4.8 mmol/L were highly specific for its diagnosis. Using a cut-off value of 3.8 mmol/L was associated with the best combination of specificity (95%) and sensitivity (72%) for DKA.

The presence of pyuria and hematuria on urinalysis, along with confirmation by examination of urine sediment supports the presence of a urinary tract infection. However, urine culture should be performed regardless of urine sediment activity.

The hemogram may be normal at presentation, but usually reveals a leukocytosis with a mature neutrophilia (common in cats), or a stress leukogram. There may be a regenerative or degenerative left shift suggestive of a severe inflammatory and/or infectious process. The red blood cell count and hematocrit may be elevated due to dehydration. Heinz bodies, with or without anemia, may be noted in cats, as feline hemoglobin is uniquely susceptible to oxidative damage.

TREATMENT

Treatment of diabetic ketoacidosis includes the following steps in order of importance: 1) fluid therapy using 0.9% saline initially, followed by 2.5% or 5% dextrose as serum glucose falls. 2) insulin therapy (low-dose intramuscular or intravenous) 3) electrolyte supplementation (potassium, phosphorus, magnesium) 4) reversal of metabolic acidosis.

Fluid Therapy

Fluid therapy should consist of 0.9% NaCl supplemented with potassium when insulin therapy is initiated; however, hypernatremic patients may be rehydrated with lactated ringers solution to limit sodium load. Placement of a large central venous catheter is preferred for intravenous access because central venous pressure (CVP) may be monitored thereby providing the means to avoid over hydration. In addition, the need for repeated venipuncture necessary for frequent monitoring of glucose, electrolytes, and blood gases is eliminated. Rapid initiation of fluid therapy is key for successful treatment of the DKA patient. Fluid rates vary depending on degree of dehydration, maintenance requirements, continuing losses such as vomiting and diarrhea, and presence of diseases such as congestive heart failure and renal disease. Extreme caution should be exercised when considering initiating fluid therapy with a hypotonic solution as this increases the risk of cerebral edema. Fluids containing dextrose may be required to maintain blood glucose concentrations as insulin treatment for the DKA is continued.

Insulin Therapy

In dogs, insulin therapy should be initiated using either intravenous insulin or low-dose intramuscular methods. Intravenous constant rate infusion (CRI) of regular insulin therapy is accomplished by placement of two catheters: a peripheral catheter for the insulin infusion, and a central catheter for sampling blood and administration of drugs and other fluids. A dosage of 2.2 U/kg for dogs or 1.1 U/kg for cats of regular (neutral, soluble) insulin is diluted in 250 ml of saline. Approximately 50 ml of fluid and insulin are allowed to run through the intravenous drip set and is discarded because insulin binds to the plastic tubing. The species of regular insulin (beef, pork or

human) does not affect response; however, the type of insulin given is very important. Regular or synthetic short acting insulin must be used; Lente, glargine, isophane or protamine zinc insulins should never be given intravenously. Using intravenous insulin administration, blood glucose decreases to below 270 mg/ by approximately 10 and 16 hours in dogs and cats, respectively. Once this has been achieved, the animal is maintained on subcutaneous regular insulin (0.1-0.4 U/kg, subcutaneously every 4-6 hrs) until it starts to eat and/or the ketosis has resolved. Often, the transition from hospital to home maintenance therapy can be made by using a low dose (1-2 U) of regular insulin combined with the intermediate or long-acting maintenance insulin at the recommended dosages.

Electrolyte and Acid Base Therapy

Potassium should be supplemented as soon as insulin therapy is initiated. While serum potassium may be normal or elevated in DKA, the animal actually suffers from total body depletion of potassium. Correction of the metabolic acidosis tends to drive potassium intracellularly in exchange for hydrogen ions. Insulin facilitates this exchange and the net effect is a dramatic decrease in serum potassium which must be attenuated with appropriate potassium supplementation in fluids. Refractory hypokalemia may be complicated by hypomagnesemia. Supplementation of magnesium along with potassium may be indicated in cats or dogs with hypokalemia that is unresponsive to potassium chloride supplementation.

Serum and tissue phosphorus may also be depleted during a ketoacidotic crisis and some of the potassium supplementation should consist of potassium phosphate (1/3 of the potassium dose as potassium phosphate), particularly in small dogs and cats who are most susceptible to hemolysis caused by hypophosphatemia. Caution should be used as over supplementation of phosphorus can result in metastatic calcification and hypocalcemia. Bicarbonate therapy may be necessary in some patients with blood pH less than 7.1 or if serum HCOs less than 12 mmol/L. Caution is recommended as metabolic alkalosis may be difficult to reverse.

HONKDM requires similar treatment to DKA but on a much slower time scale. Correct fluid and electrolyte imbalances very slowly. Fluid therapy is typically either 0.9% NaCl or 0.45% NaCl osmolality too quickly: decrease osmolality by 1/2-1 osmol/hour. The goal should be to correct dehydration over 36 hours. While patients may still be hypokalemic, this abnormality does not tend to be as severe as in DKA because they do not have as great of an osmotic diuresis. Patients with hyperosmolar diabetes may be hyperphosphatemic depending on the azotemia. Hypophosphatemia is less of a concern in HONKDM. Insulin therapy is the same as for DKA but should. These patients must be monitored very closely! Monitor urine output, electrolytes and renal values 1-3 times daily.

MONITORING RESPONSE TO TREATMENT

Fluid therapy is one of the cornerstones of treatment of the diabetic patient but over hydration is a concern, especially in cats or if renal or cardiac disease is present. With a central venous catheter in place, CVP can be monitored intermittently. Oscillometric or Doppler measurements can be used to monitor systemic blood pressure. Monitoring lead II ECGs can also be helpful not only if cardiac disease is present, but in alerting the clinician that serious electrolyte abnormalities may be developing, warranting more frequent electrolyte analyses and alteration of electrolyte replacement therapy.

Hypokalemia may cause supraventricular and ventricular arrhythmias such as premature atrial and ventricular contractions, sinus bradycardia, paroxysmal atrial or junctional tachycardia, atrioventricular block, ventricular tachycardia, and ventricular fibrillation. Other ECG changes include ST segment depression, QT prolongation and decreased amplitude and biphasic T

waves. Electrocardiographic signs of hyperkalemia include decreased P wave amplitude, prolonged PR and QRS intervals, decreased R wave amplitude, ST segment depression and increased amplitude and sharply pointed T waves, bradycardia, atrial standstill and ventricular fibrillation.

Blood glucose should be checked every one to two hours during initial therapy, especially if administering insulin via CRI or hourly intramuscular injections because hypoglycemia is a common and avoidable complication of therapy. Use of glucometers, which require only a drop of blood, allows measurement of glucose without induction of anemia. Electrolyte values can change rapidly with initiation of therapy and thus, should be monitored every 4 hours. For the first 24 to 48 hours of therapy, blood glucose concentrations should not decline below 12 mmol/L as lower values may predispose the patient to development of cerebral edema. After the first day or two, if the patient is responding to therapy, or if giving injections only every 4 to 6 hours, the frequency of blood glucose determinations can be reduced (i.e., every 4 to 6 hours). More objective measurements of hydration status include direct or indirect blood pressure measurements, as well as measuring CVP, urine output and specific gravity, body weight, serum osmolality, PCV, and total solids. Assessing the PCV and plasma for evidence of hemolysis in the hypophosphatemic patient is important to evaluate for hemolytic anemia.

Initially monitoring urine output via an indwelling urinary catheter connected to a closed system is also optimal to ensure the patient is not oliguric or anuric; this is especially important for the hyperosmolar patient as severe hyperglycemia (> 540 mg/dl) is unlikely to occur without significant renal impairment or severe dehydration and subsequent poor renal perfusion. A minimum of 1.0 to 2.0 ml urine per kilogram of body weight per hour should be produced. If output is less than optimal, check patency of the catheter, adequacy of fluid administration (CVP, arterial blood pressure, subjective signs, PCV/total solids, urine specific gravity), and adjust therapy as needed.

Serum electrolytes and blood gas analyses should be performed 4 to 6 times daily during the first 24 to 48 hours when the patient is most critical. Electrolyte composition of the fluids may need to be altered several times daily depending on results of electrolyte analyses. Performing a urine dipstick test daily is also important to assess degree of glucosuria and ketonuria. An increase in dipstick ketones may actually be indicative of successful therapy as the dipstick measures acetoacetic acid, the metabolite of the most prevalent ketone body, beta-hydroxybutyric acid.

PROGNOSIS

The prognosis for diabetic ketoacidosis in dogs is fair to good as long as the underlying disorder is treatable (urinary tract infection, pneumonia, etc). With acute pancreatitis, the prognosis depends on the severity of the pancreatic disease in both dogs and cats. Cats with hyperosmolar non-ketotic or mixed ketotic syndrome have a very poor prognosis.