Metabolic Nightmares:
Tricks for Managing Acute Renal Failure and Diabetic Emergencies

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Appropriate management of acute renal failure and diabetic emergencies requires that appropriate attention be paid to the patient's metabolic abnormalities. This lecture will discuss treatment of these two diseases with a focus on how understanding the electrolyte and acid-base abnormalities can lead to decreased morbidity and mortality.

Chloride
Chloride values must be corrected to take into account any changes in plasma free water before assessing whether or not the chloride concentration is low, normal or elevated. This is calculated by the following formula:

$[Cl^-]_{corrected} = [Cl^-]_{measured} \times 156/[Na^+]_{measured}$

The number of 156 is used in cats under the assumption that 156 mEq/L is the mean sodium concentration in cats. The number 146 should be used in dogs. This corrected value can have a significant impact on the choice of fluid therapy in certain conditions. For instance a ketoacidotic diabetic cat with a sodium of 140 mEq/L and a chloride of 118 mEq/L may become even more acidotic if 0.9% saline is infused. The corrected chloride in this situation is 131 mEq/L which is already a contributing factor to this cat's metabolic acidosis. There is a potential that this will only be worsen if 0.9% saline is infused.

Renal Failure
The primary goals of therapy are the following:
Normalize renal blood flow
Establish urine output
Normalize electrolytes and acid-base status
Diagnose the cause of the real failure and provide specific treatment
Provide nutritional support

Mean arterial blood pressure must be maintained at greater than 65 mm Hg to ensure renal perfusion. This means that both systolic and diastolic pressure must be measured. If diastolic pressure is not being measured it is essential that systolic pressures be maintained as close to normal as possible. Systolic pressures less than 110 mm Hg can be associated with mean arterial pressures less than 60 mm Hg.

Blood pressure can be normalized in most patients using fluid therapy. A combination of crystalloids and colloids should be used. In order to ensure blood volume (preload) is optimized a jugular catheter should be placed so that central venous pressure can be measured. If a jugular catheter is not an option then the jugular veins should be clipped and carefully assessed.

Fluid therapy must be closely tailored to the animals needs and should be based on cardiac status, volume status (central venous pressure), dehydration, sodium concentration, potassium concentration, albumin, and type of renal failure (polyuric, oliguric or anuric).

Dehydration should be restored using crystalloids. Generally buffered electrolyte solutions are indicated. Fluids containing potassium must be avoided in the hyperkalemic patient until urine output is restored and the potassium level is starting to decrease. Patients who are hypernatremic may require fluid with low sodium concentration. Patients who are hyponatremic are often volume overloaded and both sodium concentration and fluid rates need

to be monitored carefully. Patients who developed the dehydration rapidly should be rehydrated over 4-8 hours. Those with chronic dehydration should be hydrated over 12-24 hours. Hourly maintenance requirements should be added to this amount along with ongoing losses. Ongoing losses in patients with polyuria can be significant and urine output in these patients must be measured to ensure fluid requirements are not underestimated. Anuric patients may not even tolerate the amount of fluids required to restore dehydration until urine output is restored. If diuresis is the end goal then fluid will need to be adjusted to ensure urine output is greater than 2 ml/kg/hr.

Urine output in hypovolemic or hypotensive patients hopefully will be restored once perfusion to the kidneys is improved. If the patient is not responding several options are available. Mannitol is a hyperosmotic agent that causes an osmotic diuresis, which flushes the tubules. It also has benefits as a free radical scavenger. It is dosed at 0.25 g/kg over 15-20 minutes. This dose can be repeated if it is effective and it can be followed with a constant rate infusion at 1 mg/kg/min until it is no longer effective. It should be used with extreme caution, (and preferably not used) in patients that are hypervolemic since volume overload will result if diuresis does not result. Dextrose at 5% -20% concentrations can be used as an osmotic diuretic if mannitol is not available. The dextrose will be metabolized ultimately making this perhaps a safer choice than mannitol.

Furosemide is a loop diuretic that is most effective when given as a constant rate infusion. A bolus dose of 1-2 mg/kg can be given intravenously followed by a constant rate infusion of 1 mg/kg/hr. If there is no response after 4 hours it is less likely to be effective.

Dopamine at dopaminergic doses (0.5-3 mcg/kg/min) is designed to impact dopaminergic receptors in the kidneys and improve renal perfusion and thus renal function. There is no clear evidence this occurs. The cat lacks the appropriate dopaminergic receptors in the kidneys and one study showed no improvement in urine output, sodium excretion or glomerular filtration in cats given dopamine.

Patients in renal failure may have significant acid-base abnormalities. Acidemia related to perfusion abnormalities should correct once perfusion is restored. Dogs and cats with chronic renal failure often lose large amounts of bicarbonate in their urine due to kidney dysfunction. This is more common in the cat than the dog. These cats must be supplemented with bicarbonate or their values will never return to normal. In the author's experience these cats often require much higher doses of bicarbonate than is typically recommended. In addition the anorexia and nausea seen in cats often improves once the acidemia is improved. These cats often will require oral supplementation to maintain normal acid-base status. Bicarbonate is typically supplemented at 0.3 x kg body weight x deficit (18- measured bicarbonate level) with ¼ of this dose given over 1 hour and the remainder over the next 12 hours. If blood gas assessment is readily available this dose can be given more quickly. If blood gases are not available but total carbon dioxide levels are the bicarbonate can be estimated by the total carbon dioxide minus 1. Bicarbonate supplementation should not be provided if measured levels are not available since the side effects can seriously outweigh the benefits.

Patients in anuric renal failure will develop hyperkalemia. Hyperkalemia should be treated if it is lifethreatening as determined by evidence of significant electrocardiographic abnormalities in combination with clinical signs. Ultimately unless the animal is able to urinate the hyperkalemia will persist. If anuria persists dialysis is indicated.

Vomiting can be a substantial problem in patients with renal failure. If large volumes of fluid are being vomited a nasogastric tube should be placed for gastric decompression. This tube can then be used for delivering microenteral nutrition. Uremia triggers vomiting centrally and central acting antiemetics are likely to be the most effective at controlling vomiting. Uremia can be associated with gastric erosions and ulcerations. Administration of H-2 blockers or omeprazole and sucralfate may be indicated and are definitely indicated if there is evidence of hematemesis. Enteral nutrition has been shown to be as effective as, if not more effective than, antacids at preventing gastric ulceration. Oral ulcers are not uncommon in patients with renal failure. Oral rinses using 0.005% chlorhexidine can help prevent infection. Rinses with topical anesthetic agents have also been used anecdotally by the author to try and minimize the pain associated with the ulcers.

Nephrotoxic drugs should be discontinued and specific treatment aimed at the cause of the renal failure should be instituted as soon as possible. Hyperphosphatemia may resolve with fluid therapy; however if the hyperphosphatemia persists then phosphate binders should be administered orally once the patient is eating.

Patients with chronic renal failure may be hypertensive. Amlodipine, a calcium channel blocker, has been found to be the most effective in treating hypertension caused by renal disease. Blood pressures greater than 200 mm Hg systolic can lead to retinal detachment and should be aggressively managed.

Diltiazem has been recommended as an agent to help with renal failure associated with ischemia. It appears to decrease the intracellular calcium levels following ischemia thus decreasing the production of reactive oxygen species. It also prevents apoptosis. The dose recommended is 0.3-0.5 mg/kg over 10 minutes followed by 1-5 mcg/kg/min for 48-96 hours or as long as it takes to decrease the serum creatinine concentration to normal. The dose should be decreased if bradycardia or hypotension develops.

Angiotensin-converting enzyme (ACE) inhibitors (enalapril) are used to treat protein-losing glomerulonephropathy. The drug appears to attenuate glomerular hypertrophy and preserve glomerular function. In addition it may help control hypertension. Angiotensin-converting enzyme inhibitors should be used with caution in the acute stages of renal failure since the drug can decrease glomerular filtration rate and worsen azotemia. It can also cause hypotension and should be avoided in hypotensive patents.

Antibiotics should be administered based on culture and sensitivity results; however, occasionally, antibiotics may need to be administered without confirmation. Prophylactic antibiotics should be avoided in patients with indwelling urinary catheters since these patients are predisposed to infection and the use of antibiotics will lead to microbial resistance. Doses or dosing intervals may need to be adjusted based on creatinine levels.

Analgesics should be provide to all patients showing signs of pain. Nonsteroidal antiinflammatory agents should be avoided. Opioids should be given intravenously to effect and constant rate infusions may be required.

Diabetic Ketoacidosis

Diabetic ketoacidosis is a life-threatening complication of diabetes mellitus characterized by metabolic acidosis, hyperosmolality, and electrolyte disorders. These patients have diabetes mellitus compounded by another significant illness such as a urinary tract infection, pancreatitis, cholangiohepatitis, hyperadrenocorticism, pneumonia or an abscess leading to an increase in diabetogenic hormones such as cortisol, epinephrine, glucagon and growth hormone. The absolute insulin deficiency and insulin resistance from the secondary infection or inflammatory disorders leads to a significant cellular energy deficit. In an attempt to keep up with energy requirements the ensuing lipolysis leads to excessive hepatic production of ketoacids. The metabolic acidosis is primarily related to the ketoacids but can be complicated by a lactic acidosis that develops secondary to perfusion abnormalities. Ultimately the body's normal buffer systems are overwhelmed.

Electrolyte disorders include hyponatremia, hypokalemia, and occasionally hypomagnesemia. Hyponatremia may be due in part to the hyperglycemia but is usually compounded by urinary losses as well as the possibility of third spacing into the gastrointestinal tract or peritoneal cavity. Hypokalemia can occur secondary to loss in the urine from the osmotic diuresis as well as vomiting. The presence of hypokalemia in the face of a significant acidosis should alert the clinician to a severe total body potassium depletion which will worsen substantially when insulin therapy is instituted. The electrolyte disorders are compounded by the ketoacids which worsen the osmotic diuresis of a normal diabetic as well as the aggressive fluid therapy that is provided during treatment. In addition hypomagnesemia may develop secondary to increased free fatty acids which bind the magnesium as well as insulin which can shift magnesium intracellularly. Because measurement of serum levels (total magnesium or ionized) may not reflect total body stores, hypomagnesemia should be considered in patients with refractory hypokalemia or hypocalcemia or unexplained weakness or gastrointestinal motility abnormalities. Mild hypomagnesemia rarely causes clinical signs.

The diagnosis of diabetic ketoacidosis is made based on the history as well as laboratory findings of hyperglycemia, ketonuria and a metabolic acidosis. Patients that are known diabetics or are ketotic with normal or only mildly elevated blood glucose levels are usually in severe decompensatory shock and mortality rates are high. There are three ketoacids – acetoacetic acid, β–hydroxybutyric acid and acetone. The urine test strips only confirm the presence of acetoacetic acid and acetone as do the routine serum tests. The β–hydroxybutyrate is the most common ketoacid formed in shock states and not until insulin treatment is instituted, which converts the β–hydroxybutyric acid to acetoacetic acid, will the tests show a positive result. Blood gas results showing a metabolic acidosis with a severe base deficit but evidence of only a mild or moderate decrease in the bicarbonate concentration are consistent with unmeasured acids such as ketoacids.

The goals of treatment are to restore normal perfusion, provide insulin to ensure the cells are no longer energy deficient and the ketoacids become metabolized, correct electrolyte abnormalities, and treat any underlying additional illness.

Oxygen should be provided to patients in shock. Intravenous fluids (balanced electrolyte solution) should be provided and dehydration should be corrected over 4 to 12 hours unless the patient is at risk for fluid overload in which case hydration may need to be corrected over 24 hours. Normal saline may not be the ideal choice since the hyponatremia will correct as the glucose concentrations normalize which can lead to a hypernatremia and the chloride load can lead to a worsening of the metabolic acidosis. Synthetic colloids may be required if the patient is hypoalbuminemic secondary to concurrent disease process. Insulin therapy is generally begun several hours following initiation of fluid therapy although it may be more appropriate to start it as soon as possible. Constant rate infusions are easier to regulate than intermittent injections but require closer monitoring. Giving insulin into the intramuscular and subcutaneous tissues can lead to unpredictable uptake due to altered perfusion. This can lead to a depot effect followed by a rapid uptake of insulin at some later stage leading to significant rapid decreases in glucose levels. It would be ideal to maintain tight glycemic control with glucose levels ideally maintained between 100 and 200 mg/dl but this usually is not possible. Glucose levels should be maintained below 300 mg/dl and rapid shifts in glucose levels should be avoided in order to minimize the likelihood of causing cerebral edema. Hypokalemia secondary to intracellular fluid shifts secondary to correction of the metabolic acidosis as well as insulin therapy which drives both potassium and glucose intracellularly, is not uncommon. Hypophosphatemia can develop secondary to dilution, diuresis, and the increased production of ATP as glucose is driven intracellularly and can be a life threatening complication. Requirements for phosphorus supplementation are often much higher than what is recommended. Ultimately nutritional support will be required, preferably via the enteral route. Long acting insulin is not recommended until the patient is well hydrated and eating and the ketoacids have been metabolized. Close monitoring of these patients is essential if patient morbidity – and mortality – is to be minimized.

Hyperglycemic Hyperosmolar Syndrome

Hypoglycemic hyperosmolar syndrome or hyperosmolar hyperglycemia nonketotic syndrome is an uncommon condition that can be diagnosed in preexisting diabetics and in those who have been never been diagnosed with diabetes. It is characterized by a hyperglycemia of greater than 600 mg/dL and an osmolality of greater than 350 mOsm/L. Ketonuria is not present. Common clinical findings include severe dehydration, renal dysfunction and brain dysfunction. The disease has a very poor prognosis in large part because congestive heart failure and renal failure are frequently found in association with the syndrome.

The goal of treatment is to reduce the glucose levels slowly to avoid rapid shifts in cerebral osmolality. Idiogenic osmoles have developed over time in the brain to counteract the effects of the hyperglycemia; therefore, if the plasma osmolality is decreased too rapidly cerebral edema will develop. Hyponatremia is commonly found in association with hyperglycemia. This is a normal physiologic response by the body to the hyperosmolality although other causes for hyponatremia must be ruled out. Changes of greater than 1 mEq/hr in the plasma sodium concentration should be avoided so close monitoring of electrolytes (hourly initially) is essential. Fluid therapy should be tailored according to the response of the patient to treatment. The cornerstone of therapy is to

increase the glomerular filtration rate to allow the kidneys to filter the glucose. Due to the fact that heart disease and renal disease are often present in these patients, high fluid rates are often not tolerated making management of this condition complicated. If the patient is not tolerant of high rate intravenous fluid therapy, enteral fluid therapy may also need to be initiated. Insulin therapy should be instituted once the patient is rehydrated. The recommended starting dose is 50% of that used for treatment of diabetic ketoacidosis.

Hypoglycemic Crisis

Severe hypoglycemia can occur in diabetics that have been overdosed with insulin. The overdose may be an acute problem where the patient is double-dosed inadvertently. It is also associated with an inadequate decrease in the face of decreased food intake or a Somogyi effect. The latter is very common when glucose curves are not being performed and insulin doses are increased based solely on the finding of a single elevated blood glucose level or when changes in insulin dosing are based on laboratory results as opposed to clinical status (i.e., resolution of polyuria, polydipsia and weight loss. In cats it can occur when the animal reverts back spontaneously to being a non-diabetic or a non-insulin-dependent diabetic.

The brain is an obligate user of glucose and has a very poor ability to use other energy sources, nor does it have a significant store of glycogen. This means that neural tissue can be severely and sometime permanently damaged by neuroglycopenia. The degree of damage will depend on the severity of the hypoglycemia as well the duration of the hypoglycemia. Abnormal mentation, seizures and blindness can persist even after resolution of the hypoglycemia.

Hypoglycemic patients should receive an intravenous bolus of 1-2 ml/kg of 25% dextrose. This should be followed immediately with a constant rate infusion of 2.5% to 5% depending on the severity of the hypoglycemia. If seizure activity does not resolve a blood glucose level should be checked immediately since hypoglycemia may not be the sole cause of the seizure activity. A blood glucose level should be checked within 15 minutes to ensure the patient's glucose has normalized. If it is still low another bolus should be given and the infusion should be increased by 2.5%. This process should be repeated until the blood glucose has normalized. Some patients may require 10% dextrose infusions. Infusions of greater than 5% dextrose ideally should be administered via central lines due to the hyperosmolality. If placement of a central line is not an option then the smallest gauge catheter possible should be inserted. This should improve the blood flow around the catheter relative to one of a larger diameter which should help decrease the likelihood that phlebitis will develop.

References available on request.