CHAPTER 6

DIABETIC KETOACIDOSIS

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Originally described by Dreschfeld in 1886, diabetic ketoacidosis (DKA) is an urgent metabolic derangement of diabetes mellitus.[1] Occurring in patients with insulin-dependent diabetes much more frequently than non-insulin dependent diabetes, DKA is responsible for just under 10% of diabetic hospitalizations each year.[2] It is estimated that newly diagnosed IDDM accounts for only 20% of ketoacidotic episodes.[3] That leaves the vast majority of hospital admissions due to this crisis represented by known diabetic patients. Although the mortality rate has decreased exponentially with the advent of insulin and further understanding of the disease process, continued patient education and awareness is paramount.

PRECIPITATING FACTORS

As is commonly the case with complications of diabetes, poor patient compliance plays a significant role in the development of diabetic ketoacidosis. Many episodes of DKA are recurrent in nature lending substantiation to poor compliance. In fact, an estimated 20% of annual ketoacidotic incidents occur at regular intervals.[4] The most frequent precipitating event is infection.[5] This is accompanied by insulin insufficiency, inadequate water intake, drug use, and various coexisting medical conditions. The stresses caused by all of these pressing situations can spur the onset of DKA especially in the setting of increased age and compromised medical status.

PATHOGENESIS

Diabetic ketoacidosis develops as a complication of acute insulin deficiency with resultant hyperglycemia and increased levels of the insulin counterregulatory hormones: epinephrine, cortisol, and glucagon. The three main insulin-sensitive tissues are the liver, muscle and fat. In the setting of DKA, a severe stress state is created and these tissues forego the use of glucose. Therefore, a condition of metabolic catabolism ensues.[6] Proteins are broken down to amino acids in muscle cells. Adipose tissue carries out hydrolysis of fat to triglycerides that undergo further lipolysis to free fatty acids (FFA) and glycerol. The accumulation of large quantities of these breakdown products, amino acids, FFA and glycerol, accompanied by increased levels of the counterregulatory hormones in the plasma affect the overall metabolic processes of the liver. Gluconeogenesis, the production of glucose from noncarbohydrate precursors, is stimulated by these plasma level alterations releasing massive amounts of glucose into the circulation compounding the hyperglycemia. Glucose production is also continued in the liver via the pathway of glycogenolysis, the breakdown of liver glycogen stores to glucose. Again the altered plasma levels, mainly increased glucagon and epinephrine along with decreased insulin, expedite this pathway. As is clearly evident, the hyperglycemia is a combination of overproduction and under utilization by peripheral tissues with overproduction contributing to a greater degree.

Ketogenesis is the process by which ketone bodies, acetoacetate, ß-hydroxybutyrate and acetone, are formed in the liver. Ketone bodies can be utilized as alternate sources of energy by extrahepatic tissues. However, in DKA the altered metabolism forces the overproduction of ketones which surpasses the rate of their use as ketogenesis is tightly coupled to gluconeogenesis.[4] The continuous high concentration of FFA provides the necessary substrate for maintained ketoacid production. In addition, the glucagon:insulin ratio is increased and the rate of liver ketogenesis has been shown to correlate directly to plasma glucagon concentration in the setting of insulinopenia.[7] Because these ketone bodies are strong acids, buffering by bicarbonate and buffering proteins occurs resulting in metabolic acidosis.

Loss of water and electrolytes in DKA is a result of hyperglycemia induced osmotic diuresis. The elevated blood glucose levels lead to a state of hyperosmolality and glucosuria. Initially, the loss of fluid from the intracellular to extracellular compartment causes dilution of plasma electrolyte concentrations. With continued hyperglycemia, the threshold for renal glucose reabsorption is exceeded and an increased glomerular filtration rate occurs. Eventually, loss of electrolytes and water leading to severe volume depletion results. Retention of glucose and ketoacids accompanies a decreased glomerular filtration rate in such hypovolemia.[4] In this setting, blood glucose concentrations can reach 500mg/dL or more and ketoacidosis is marked.[3] Due to the osmotic diuresis, a total body potassium deficit is present. Compounding the low potassium levels is the lack of insulin-induced entry into cells due to existing insulinopenia.[8]

DIAGNOSIS

A definitive diagnosis of diabetic ketoacidosis requires three specific criteria: 1) hyperglycemia (>250 mg/dL), 2) low bicarbonate (<15mEq/L), and 3) low pH (<7.3) with ketonemia (+ at 1:2 dilution) and moderate ketonuria.[3] Hyperglycemia has already been discussed but it has been reported that about 15% of DKA patients possess blood glucose <350mg/dL by finger stick. Arterial blood gases must confirm metabolic acidosis through arterial pH and bicarbonate concentrations. The metabolic acidosis of DKA shows an increase in anion gap [Na - (Cl +HCO3] though there is often a component of added hyperchloremic acidosis. The presence of ketones in the blood and urine can be proven via the nitroprusside reaction. However, this test often correlates poorly with the degree of ketonemia because betahydroxybutyrate does not react with the nitroprusside reagent.[4] Despite a total body potassium deficit in the range of 5mEq/kg body weight, hyperkalemia may be associated with DKA as potassium moves from the intracellular to extracellular compartment.[6]

Signs and symptoms of DKA begin with subtle changes such as polyuria and polydipsia. The presence of conventional symptoms such as nausea, vomiting and marked fatigue also occur. Other common findings upon presentation of DKA are a fruity odor of the breath caused by acetone and abdominal pain as a result of hyperamylasemia. Postural hypotension with tachycardia is indicative of severe dehydration and salt depletion. With progression of DKA, mental stupor and coma can result.[9] The severe acidotic state stimulates the respiratory center leading to rapid, deep respiration known as Kussmaul breathing.[8]

Initial evaluation should commence with a concise history and rapid physical exam. Lab tests consisting of blood chemistries, complete blood count with differentials, finger stick for blood glucose, nitroprusside reaction for ketones, arterial blood gases and urinalysis should be performed immediately. Other labs relating to individual specific conditions should also be ordered as deemed necessary.

Treatment

Successful outcomes in the treatment of DKA demand intense supervision and careful attention to patient status. Goals of therapy include restoration of volume and electrolyte deficiency, reduction of hyperglycemia, and resolution of serum and urine ketone levels. Significantly decreased mortality is the result of now widely accepted routine treatment guidelines.

The first priority in DKA treatment is reversal of hypovolemia via hydration therapy. This is carried out by immediate administration of one liter of normal saline solution (0.9% NaCl) over the first hour. Normal saline stays in the extracellular space replacing the fluid lost to osmotic diuresis.[3] Half normal saline may be used initially in the case of severe hypernatremia (>150mEq/dL) and is the fluid of choice following the first liter of NSS under normal treatment conditions.[6] This is due to half normal saline contributing to replenishment of both intra and extracellular fluid. The overall effects of rehydration are increased circulatory volume, decreased counterregulatory hormones, and decreased blood glucose concentrations via increased urinary excretion and extracellular dilution. Other fluids used in rehydration consist of colloid solutions in the setting of shock and dextrose solutions to avoid severe hypoglycemia.[6]

Insulin treatment is mandatory in the reversal of DKA. Despite historical treatment regimens implementing very large doses of insulin, smaller doses of insulin are now the standard of care. The use of extremely large doses of insulin are consistent with prolonged action resulting in hypokalemia and hypoglycemia. Such doses of insulin were thought to combat "insulin resistance" among patients with DKA. It is now known that all patients exhibit some degree of resistance to insulin due to peripheral dispersion of glucose, high concentrations of counterregulatory hormones, acidemia and phosphorus deficiency.[3] Today's treatment regimens implement a priming dose of 0.4 U/kg body weight with half administered as an IV push and the remaining as subcutaneous injection for conscious patient's. Those presenting in a coma receive 7 U/hour by continuous IV infusion. Subsequent insulin therapy is based on plasma glucose concentrations. Dosing consists of either repeating the priming dose or doubling the infusion rate if glucose does not decrease by 10% in the first hour. If adequate glucose decrease is obtained, continued therapy depends on location of patient receiving treatment. General hospital ward patients should be dosed with 7 U/h subcutaneously to ensure necessary monitoring while continuous intravenous infusion of 7 U/h is preferred for patients in the intensive care unit.[6] The average rate of blood glucose reduction is 75-100mg/dL/hr at the doses described above. This ensures therapeutic levels in 6-8 hours.[3] Despite desired blood glucose, insulin therapy must not be decreased until full resolution of persistent ketoacidosis. Dextrose solutions become increasingly important as the blood glucose reaches concentrations close to 200mg/dL in order to ensure the absence of hypoglycemia.

Electrolyte abnormalities must be monitored during

the concomitant fluid and insulin regimen. Sodium deficiencies are corrected via the administration of saline solutions while increasing fluid volume. As mentioned above, normal and/or half normal saline solutions are employed. A rapid decline in plasma potassium levels occurs with initial hydration and insulin therapy due to plasma dilution and insulin-mediated entry of potassium intracellularly.[9] To prevent the life-threatening settings of severe hypokalemia or hyperkalemia, potassium is administered after the initial fluids and insulin have shown patient improvement. Potassium is supplied in the form of 20-30 mEq/L with two-thirds KCl and one third KPO4. Bicarbonate supplementation is of no benefit to the treatment regimen in DKA and carries potential dangerous disadvantages.[6] Phosphate deficiencies are supplemented along with potassium in the form of potassium phosphate. Additional phosphate administration demonstrates no clinical benefits and could lead to adverse effects.[6]

SUMMARY

Although insulin dependent diabetes accounts for only 5-10% of diabetes mellitus cases, the vast majority of diabetic ketoacidotic crises are represented by this group of patients. Treatment has been bettered over the past 30 years to a point in which mortality is less than 5%. With over 90,000 admissions having a primary diagnosis of DKA in 1996, the incidence of fatality is not to be taken lightly.[2] Enhanced education and a team approach to treatment and prevention of diabetes complications will allow continued future success.

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