Quiz of the Month

Answers

(1) Arterial pH 7.15 and PaCO₂ 21 mm Hg are characteristic of a metabolic acidosis. His serum anion gap (AG) is 30 mmol/l (135 - 101 mmol/l), a normal AG being 16 ± 4 mmol/l. A high-AG metabolic acidosis must be caused by accumulation of organic acid anions such as lactate or ketone bodies or ingestion of an organic acid like salicylate, cyanide, methanol (metabolized to formaldehyde and formic acid), paraldehyde, or ethylene glycol. In view of the presence of ketones in the urine and lactate in the blood, the most likely cause of the high-AG metabolic acidosis is a combined ‘alcoholic’ ketoacidosis and lactic acidosis.

Assuming his acid-base status had been normal prior to the present illness [HCO₃⁻] 25 mmol/l and AG 16 mmol/l), the A[HCO₃⁻] is 18 mmol/l and the AAG 14 mmol/l. The 4-mmol/l discrepancy between the A[HCO₃⁻] and the AAG is likely due to the presence of another acid-base disturbance – either a normal-AG metabolic acidosis or a primary respiratory alkalosis. The diarrhea that accompanied the present illness would seem the most likely cause of a normal-AG metabolic acidosis, since he had not been drinking battery acid. A renal acidification defect associated with hypokalemia and a urine pH less than 5.5 (e.g., proximal renal tubular acidosis) would be unusual. The most likely cause of hyperventilation in a nonhypoxemic cirrhotic patient is the cirrhosis itself, which is associated with high circulating levels of ammonia and progesterone and with arteriolovenular shunting in the brain and lungs.

(2) Alcoholic patients may present with ketosis caused by starvation, diabetic ketoacidosis (when severe pancreatic damage has led to endocrine insufficiency), or withdrawal from ethanol after a prolonged drinking binge. Because ethanol suppresses hepatic ketogenesis by inhibiting lipolysis, alcoholics usually do not develop ketoacidosis as long as they keep drinking. However, those whose only exogenous source of calories has been ethanol for more than a day are at risk of developing starvation ketosis whenever ethanol consumption is curtailed for 24-48 h, such as by vomiting, gastritis, pancreatitis, or other causes. Since this form of ketoacidosis is in reality nothing more than starvation ketosis that had been suppressed by ethanol and unmasked by ethanol withdrawal, it should properly be known as ‘ethanol withdrawal/starvation’ ketoacidosis rather than by the commonly used but misleading name ‘alcoholic’ ketoacidosis.
In a prolonged fast, glucose levels fall, insulin is suppressed, glucagon is stimulated, and the serum insulin:glucagon ratio falls. A low insulin:glucagon ratio induces lipolysis in adipose tissue and protein hydrolysis in muscle to increase delivery of fatty acids and amino acids to the liver where they are used, respectively, as energy substrates and the precursors of the 3-carbon building blocks for gluconeogenesis. In the liver the low insulin:glucagon ratio suppresses glycogen synthesis, glycolysis, and production of malonyl coenzyme A (CoA), while it stimulates gluconeogenesis and carnitine availability. Low levels of malonyl CoA and high levels of carnitine stimulate transport of fatty acid derived palmitoyl CoA into the mitochondria via carnitine palmitoyl transferase I. In the mitochondria, palmitoyl CoA is changed to acetyl CoA and thence to P-hydroxy-(3-methylglutaryl)CoA and finally to acetoacetic acid. Acetoacetic acid is reduced by NADH + H+ to (3-hydroxybutyric acid and NAD+ in tissues containing (3-hydroxybutyrate dehydrogenase and is converted nonenzymatically to acetone.

The keto acids, acetoacetic and (3-hydroxybutyric, together with acetone comprise the ketone bodies. Keto acids are buffered by extracellular fluid bicarbonate, while a portion of the undissociated, protonated keto acid diffuses into the cells and is metabolized to bicarbonate. The sodium salts of the keto acids, unlike acetone, are readily filtered by the glomerulus, poorly reabsorbed by the renal tubule, and rapidly cleared from the blood as long as renal perfusion and function are intact, while their appearance in the urine increases the urinary AG. The plasma AG also increases as bicarbonate is replaced by unmeasured keto anion. The AAG:A[HCC > 3] ratio in uncomplicated ketoacidosis is therefore 1.1:1, as long as urinary excretion of ketones is impaired by volume contraction.

Ethanol withdrawal ketoacidosis is more prevalent in women, and some patients are prone to repeated attacks. Typically, initial laboratory tests reveal increased serum ketones and mild hyperglycemia. However, the nitro-prusside test for ketones may initially be either negative or positive at low titer, due to the predominance of (3-hydroxybutyrate. The blood glucose may be low whenever glycogen stores have been depleted by prolonged fasting, since alcohol both inhibits gluconeogenesis (by increasing the NADH:NAD+ ratio) and potentiates the action of insulin. The marked AG in ethanol withdrawal ketoacidosis usually results from increased (3-hydroxybutyrate, not from ethanol itself, with only mild to moderate elevations in serum lactate, unless the liver’s ability to convert organic acids to bicarbonate has been compromised by hepatitis, steatosis, cirrhosis, underperfusion (e.g., severe volume contraction, congestive heart failure, or sepsis), hypoxemia (e.g., convulsions, pneumonia, or adult respiratory distress syndrome), drugs (e.g., biguanides, salicylates, paraldehyde, nitroprusside, fructose, sorbitol, xylitol, isoniazid, streptozotocin, epinephrine, or norepinephrine), toxins (e.g., methanol, ethylene glycol, or cyanide), or other illnesses (e.g., diabetes mellitus, disseminated intravascular coagulation, vasculitis, liver failure, neoplastic diseases, renal failure, iron deficiency, or short-bowel syndrome). In this case the lactic acidosis is probably exacerbated by volume depletion that has compromised hepatic perfusion and alcoholic steatosis that has inhibited liver function.

Oxidation of 1 mol of ethanol to acetaldehyde and then to acetic acid consumes 2 mol of NAD+ and generates 2 mol of NADH + H+. Elevated of the NADH:NAD+ ratio is held responsible for increasing hepatocellular oxygen demand and hypoxic damage, inhibition of mitochondrial pyruvate carboxylase, stimulation of lactate dehydrogenase, inhibition of gluconeogenesis, and increased lactate and (3-hydroxybutyrate production. The ratio of serum P-
hydroxybutyrate:acetoacetate, normally 3 or 4:1, is characteristically increased, up to 9:1 because of the high NADH:NAD+ ratio. The mild lactic acidosis of ethanol intoxication decreases renal urate secretion and induces hyperuricemia. Ethanol withdrawal ketoacidosis is easily treated with glucose, saline, and small amounts of alkali. Ethanol intoxication may be associated with a variety of other acid-base disturbances (e.g., mild acetic acidosis, cirrhosis-related respiratory alkalosis, or vomiting-related metabolic alkalosis) and is not infrequently complicated by gastrointestinal bleeding, bacterial infection, acute pancreatitis, seizures, delirium tremens, liver failure, hyperuricemia, initial hyperphosphatemia followed by hypophosphatemia after a few days of feeding, and hypoglycemia. (3) An osmolar gap is present whenever the plasma osmolality (Posm) measured by freezing point depression (not vapor pressure elevation) exceeds that calculated by the formula

\[ \text{Posm} = 2([\text{Na}^+] + [\text{K}^+]) + ([\text{glucose}] - 100)/18 + (\text{BUN} - 20)/2.8 + 15 \]

The simultaneous findings in an alcoholic of severe acidosis and a large osmolar gap suggest methanol intoxication, in which case the acidosis is caused by formic acid, while formaldehyde may cause weakness, nausea, headache, blindness, coma, and death within 12-36 h. Ethylene glycol ingestion, producing lactate, glycolate, gly-oxalate, oxalate, formate, and hippurate, may cause a profound, life-threatening metabolic acidosis and neurologic symptoms ranging from drunkenness to coma during the first 12 h after ingestion of antifreeze, followed by cardiopulmonary dysfunction, flank pain, oliguria, and anuric renal failure from calcium oxalate crystaluria. The osmolar gap in ethylene glycol intoxication ranges from 11 to 34 mosm/kg. Severe intoxication with either methanol or ethylene glycol usually requires aggressive treatment with intravenous bicarbonate, intravenous or oral ethanol to block alcohol dehydrogenase, and hemodialysis.

References


