Alcoholic Ketoacidosis

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Background

In 1940, Dillon and colleagues first described alcoholic ketoacidosis (AKA) as a distinct syndrome. AKA is characterized by metabolic acidosis with an elevated anion gap, elevated serum ketone levels, and a normal or low glucose concentration.[1, 2]

Although AKA most commonly occurs in adults with alcoholism, it has been reported in less-experienced drinkers of all ages. Patients typically have a recent history of binge drinking, little or no food intake, and persistent vomiting.[3, 4, 5] A concomitant metabolic alkalosis is common, secondary to vomiting and volume depletion (see Workup).[6]

Treatment of AKA is directed toward reversing the 3 major pathophysiologic causes of the syndrome, which are:

- Extracellular fluid volume depletion
- Glycogen depletion
- An elevated ratio of the reduced form of nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD^+)

This goal can usually be achieved through the administration of dextrose and saline solutions (see Treatment).

Pathophysiology

importance / nécessité des vomissements importants

The pathogenesis of AKA is complex.[7] Although the general physiological factors and mechanisms leading to AKA are understood, the precise factors have not been fully defined. The following are the 3 main predisposing events:

- Delay and decrease in insulin secretion and excess glucagon secretion, induced by starvation
- Elevated ratio of the reduced form of nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD^+) secondary to alcohol metabolism
- Volume depletion resulting from vomiting and poor oral intake of fluids

The body decreases insulin activity in the starvation state and increases the production of counter-regulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone. Hormone-sensitive lipase is inhibited by insulin, and, when insulin levels fall, lipolysis is up-regulated, causing the release of free fatty acids from peripheral adipose tissue.

Free fatty acids are either oxidized to CO_2 or ketone bodies (acetoacetate, hydroxybutyrate, and acetone), or they are esterified to triacylglycerol and phospholipid. Carnitine acyltransferase (CAT) transports free fatty acids into the mitochondria and therefore regulates their entry into the oxidative pathway. The decreased insulin-to-glucagon ratio that occurs in starvation indirectly reduces the inhibition on CAT activity, thereby allowing more free fatty acids to undergo oxidation and ketone body formation.

Prolonged vomiting leads to dehydration, which decreases renal perfusion, thereby limiting urinary excretion of ketoacids. Moreover, volume depletion increases the concentration of counter-regulatory hormones, further stimulating lipolysis and ketogenesis.

Metabolism of ethanol

The metabolism of alcohol itself is a probable contributor to the ketotic state. Alcohol dehydrogenase metabolizes alcohol to acetaldehyde in the cytoplasm of hepatocyte mitochondria. Acetaldehyde is metabolized further to acetic acid by aldehyde dehydrogenase. Both steps require the reduction of nicotinamide adenine dinucleotide (NAD^+) to reduced nicotinamide adenine dinucleotide (NADH). Thus, NAD^+ is consumed and NADH is generated.

The resulting increase in the NADH/NAD^+ ratio inhibits hepatic gluconeogenesis and elevates the ratio of hydroxybutyric acid to acetoacetic acid. Acetic acid is converted by coenzyme A to acetyl-coenzyme A, which in turn is used for the conversion to adipose tissue, in the formation of ketone bodies, and in the citric acid cycle.

The decreased ratio of NAD^+ to NADH has the following implications:

- Impaired conversion of lactate to pyruvate with an increase in serum lactic acid levels
- Impaired gluconeogenesis because pyruvate is not available as a substrate for glucose production
- A shift in the hydroxybutyrate (β-OH) to acetoacetate (AcAc) equilibrium toward β-OH

In contrast to diabetic ketoacidosis, the predominant ketone body in AKA is β-OH. Routine clinical assays for ketonemia test for AcAc and acetone but not for β-OH. Clinicians underestimate the degree of ketonemia if they rely solely on the results of laboratory testing.

Dehydration

All patients with severe AKA are dehydrated. Several mechanisms are responsible for dehydration, including protracted vomiting, decreased fluid intake, and inhibition of antidiuretic hormone secretion by ethanol. Volume depletion is a strong stimulus to the sympathetic nervous system and is responsible for elevated cortisol and growth hormone levels.

Dehydration and volume constriction directly decrease the ability of the kidneys to excrete ketoacids. Profound dehydration can culminate in circulatory collapse and/or lactic acidosis.

Fasting

Energy (caloric) restriction secondary to abdominal pain, nausea, or vomiting usually occurs prior to the onset of AKA.[6] Under conditions of starvation, the liver increases the production of ketones from fatty acids to supply the brain, kidney, and other peripheral tissues with a metabolic fuel that can replace glucose. Increased ketogenesis secondary to the utilization of hepatic glycogen stores, with subsequently increased lipolysis and a decreased insulin-to-glucagon ratio, causes starvation ketosis.

Triglycerides stored in adipose tissue undergo lipolysis and are released into the circulation as free fatty acids bound ionically to albumin. Free fatty acids are removed by the liver, where they primarily undergo oxidation to hydroxybutyric acid and acetoacetate and subsequently are reesterified to triglyceride. Decreased insulin and elevated glucagon, cortisol, catecholamine, and growth hormone levels can increase the rate of ketogenesis.

Ketogenesis

Increased availability of free fatty acids, which provide the major substrate for ketone body formation, stimulates ketogenesis. Low insulin levels and elevated glucagon, catecholamine, growth hormone, and cortisol levels provide a hormonal milieu that inhibits the hepatic metabolism of acetyl-coenzyme A via the citric acid cycle and triglyceride synthesis, resulting in ketogenesis. In AKA, the increased ratio of NADH/NAD^+ increases the proportion of beta hydroxybutyrate relative to acetoacetate.[4, 8]

Ketone body clearance is decreased by 2 major mechanisms, as follows:

- The low insulin level characteristic of AKA prevents ketone body utilization by insulin-sensitive tissues
- Dehydration impairs the excretion of ketones by the kidneys

Elevated cortisol levels can increase fatty acid mobilization and ketogenesis. Growth hormone can enhance precursor fatty acid release and ketogenesis during insulin deficiency. Catecholamines, particularly epinephrine, increase fatty acid release and enhance the rate of hepatic ketogenesis.

Insulin release from the pancreatic beta cells might be abnormally sensitive to catecholamine inhibition. The pivotal variable appears to be a relative deficiency of insulin. Individuals with higher insulin levels are more likely to present with the syndrome of alcohol-induced hypoglycemia without ketoacidosis.[9]

Etiology

Most cases of AKA occur when a person with poor nutritional status due to long-standing alcohol abuse who has been on a drinking binge suddenly decreases energy intake because of abdominal pain, nausea, or vomiting. In addition, AKA is often precipitated by another medical illness such as infection or pancreatitis.

AKA results from the accumulation of the ketoacids, hydroxybutyric acid, and acetoacetic acid.[4, 8] Such accumulation is caused by the complex interaction stemming from alcohol cessation, decreased energy intake, volume depletion, and the metabolic effects of hormonal imbalance.

Epidemiology

The prevalence of AKA in a given community correlates with the incidence and distribution of alcohol abuse in that community. No racial or sexual differences in incidence are noted.

Age-related differences in incidence

AKA can occur in adults of any age; however, it most often develops in persons aged 20-60 years who are chronic abusers of alcohol. Rarely, AKA occurs after a binge in persons who are not chronic drinkers. Recently, a case report was published of an 11 year-old boy who presented in AKA after drinking ethanol-based mouthwash.[10]

Prognosis

With timely and aggressive intervention, the prognosis for a patient with AKA is good. The long-term prognosis for the patient is influenced more strongly by recovery from alcoholism.

Mortality and morbidity are rare in uncomplicated AKA. The major cause of morbidity and mortality in AKA is not the acidosis itself but is instead the inadequate treatment of concurrent medical or surgical conditions, such as gastrointestinal bleeding and alcohol withdrawal.[1, 4, 11] Complications occur in less than 20% of patients

Mortality is rare; however, alcoholic ketoacidosis (AKA) has been reported as the cause of death in a number of alcoholics. Markedly elevated beta hydroxybutyric acid could lead to death.[4, 8]

Patient Education

Refer the patient for treatment of chronic alcohol abuse. For patient education information, see the Mental Health and Behavior Center, as well as Alcoholism and Alcohol Intoxication.

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