Case Report

The fatal booze!—triple acid–base disorder in a patient with alcohol intoxication

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Abstract

Patients of chronic alcohol abuse can present with a variety of acid-base disorders and electrolyte disturbances. Lactic acidosis (LA) along with alcoholic ketoacidosis is an infrequent and underappreciated cause of wide anion-gap metabolic acidosis in alcoholic patients. The likelihood of misdiagnosing the condition is high because of the lack of awareness and presence of nonspecific clinical signs and symptoms shared with other clinical abnormalities such as acute pancreatitis, methanol or ethylene glycol poisoning, and diabetic ketoacidosis, which exist in these patients. As this condition is reversible with early intervention, promptly recognizing the condition and initiating proper treatment by the physicians would go a long way in preventing the morbidity and mortality in these patients. The outcome for such patients is excellent with early intervention. We report a patient with history of chronic alcoholism and alcohol binge admitted to the emergency department with triple acid–base disorder, which included life-threatening high anion-gap metabolic acidosis owing to concomitant LA and alcohol-related ketoacidosis in which the primary element was LA along with metabolic and respiratory alkalosis.

KEY WORDS: Anion-gap metabolic acidosis, lactic acidosis, alcohol-related ketoacidosis, alkalosis

Introduction

Alcoholism is a major issue globally. Its prevalence in India has been calculated at 30% (Benegal et al., 2000). Individuals with history of chronic alcoholism frequently have a constellation of acid–base, fluid, and electrolyte abnormalities, which play a significant role in their morbidity and mortality. In chronic alcoholism, an abrupt cessation or reduction of alcohol consumption leads to the development of alcoholic ketoacidosis (AKA), which is a poorly diagnosed medical emergency and a common cause for admission to the emergency departments. In an autopsy study of alcoholic persons, it was the cause of death in 7% of cases.[1] AKA is characterized by increased anion-gap metabolic acidosis. Less commonly described cause of high anion-gap metabolic acidosis in alcoholics is lactic acidosis. Severe lactic acidosis following only ethanol intoxication is rarely described in literature. We report a case of a chronic alcoholic patient who had primary wide anion-gap metabolic acidosis (concomitant severe lactic acidosis and ketoacidosis) caused by alcohol intoxication coupled with thiamine deficiency and concurrent respiratory and metabolic alkalosis, thus highlighting the complexity of metabolic derangements in persons with chronic alcohol abuse.

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Case Report

A 30-year-old male patient, driver by occupation, unmarried was admitted in the intensive care unit (ICU) with complaints of breathing difficulty and several episodes of vomiting of 1 day duration. There was no abdominal pain, loose stools, or fever. Patient was a chronic alcoholic person for the past several years and would consume more than 100 g of indigenously made alcohol (locally called hadia) every day. He admitted to drinking large amount of alcohol during the previous 2 days but denied to ingesting any other toxic substance. During the last 48 h before admission, he had not taken food

at all. There was no history of significant medical ailment except alcohol abuse.

On admission, he was thin built, oriented to person but not to time and place, and showed mild pallor, and his breath revealed a strong smell of alcohol. There was dehydration, no jaundice, pedal edema, clubbing, and lymphadenopathy. He was afebrile, respiratory rate was 36/min, pulse was 110/min, and regular and blood pressure in supine position was 128/84 mm Hg. Examinations of cardiovascular, respiratory system, abdomen showed normal findings. Examination of central nervous system revealed slightly confused state with normal sized pupils, reacting to light, no nystagmus, no ophthalmoplegia, no focal neurological deficit, and soft neck. His random blood sugar on admission was 54 mg/dL. His complete blood picture revealed hemoglobin 12.6 g/dL, MCV 98 fl, total leukocyte count of 11,300/mm^3 with 78% neutrophils, 20% lymphocytes, and 2% monocytes, and platelet count of 1.78 lakhs/mm^3. His blood urea nitrogen (BUN) and serum creatinine were 76 and 0.8 mg/dL, respectively, while liver function tests showed total serum bilirubin 1.2 mg/dL, ALT 152 U/L, AST 859U/L, ALP 92 U/L, GGT 168 U/L, serum albumin 3.2gm/dL, serum globulin 3.8 g/dL and PT (INR) 1.4. His serum sodium, potassium, and ionized calcium were 128 mmol/L, 4.3 mmol/L, and 0.6 mg/dL, respectively. His serum osmolality measured on admission was 318 mOsm/kg of H_2O, serum for ketones was nil, and blood alcohol level was 78 mg/dL. A urinalysis showed a specific gravity of 1.017, a pH of 5, large ketone bodies (3+), and no glucose, cells, or crystals. Serum amylase and lipase were normal. Chest radiograph was normal. Ultrasound of whole abdomen revealed grade I fatty liver with cholelithiasis. Electrocardiogram showed sinus tachycardia with prolonged QT_C interval. His arterial blood gas (ABG) done on admission with ABL800 Basic while breathing room air showed pH 6.907, PCO_2 7 mm Hg, PO_2 131mm Hg, HCO_3^- 4.1 mmol/L, and blood lactate 21 mmol/L (normal range: 0.7–2.1 mmol/L) suggestive of severe high anion-gap metabolic acidosis with anion gap of 44.2 mmol/L (normal range, 12 ± 2 mmol/L). A final diagnosis of ethanol-related acute hepatitis with high anion-gap metabolic acidosis owing to mixed lactic acidosis and alcohol-related ketoacidosis, associated with metabolic alkalosis and respiratory alkalosis, electrolyte imbalance, and hypoglycemia was made. His serial ABGs during hospital study are shown in Table 1. His blood for toxic alcohol screen was not sent as the test is not available in our hospital.

His hypoglycemia was corrected with l00 mL of 25% dextrose solution. He was volume depleted on admission, owing to repeated vomiting and poor fluid intake during the last 48 h. This was evident by hypochloremia and the fall in the hematocrit from 38 to 27 the morning after admission, following replacement of intravenous fluids. The patient was given a bolus of 100 mg of thiamine and 1,000 mL of 0.9% NaCl over 1 h, followed by 1,000 mL of 5% dextrose/0.9% normal saline with 1 vial of multivitamins over 6 h and 100 mmol sodium bicarbonate over 4 h. He was also given pantoprazole (40 mg od), metochlorpromide (10 mg tid) and haloperidol (5 mg sos) intravenously. His ABG repeated at 8 h after admission still showed blood lactate of 17 mmol/L. He was subjected to hemodialysis owing to persistent metabolic acidosis. Bicarbonate-based dialysis was done. His ABG done 16 h after hemodialysis showed significant decrease in lactate from 17 to 9.5 mmol/l. As the acidosis was getting corrected, hypokalemia was evident, which was treated with initial intravenous infusion of 120 mmol over initial 12 h, followed by oral supplementation. Improvement in the parameters continued, and by third day, he was asymptomatic. On fourth day, his arterial pH was 7.35, blood lactate level was 1.9 mmol/L, and anion gap nearly normalized. His liver enzymes showed a decreasing trend, and he was discharged on the fifth day when his metabolic parameters normalized [Figure 2] with advice to continue oral ranitidine (150 mg BD) and thiamine (100 mg/d for 7 days).

Discussion

Lactic acidosis is defined as large anion-gap metabolic acidosis with arterial pH less than 7.35 and lactate level greater than 5 mmol/L. In critically ill patients, it is associated with serious underlying pathologic conditions. The prevalence is estimated to be approximately 1% of all the hospitalized non-surgical patients.[2] Our patient was admitted to ICU with very severe, life-threatening wide anion-gap metabolic acidosis following an alcohol binge. However, acidosis of this degree is distinctly uncommon following ethanol ingestion alone. In a study by Halerpin et al.[3] of 10 alcohol-dependent patients with 13 episodes of metabolic acidosis, the average arterial pH was 7.29 and serum lactate level was 7.3 mmol/L.[3] Four other case reports of lactic acidosis in nondiabetic alcoholic patients are documented where serum lactate levels were 7, 1, 6, and 3 mmol/L, respectively.[4–7]

Thus, on the basis of the severity of patient's metabolic acidosis, the possibility of ingestion of toxic alcohols such as methanol, ethylene glycol, isopropanol was considered. This was supported by the evidence of a high plasma osmolal gap, which is the difference between the measured plasma osmolality in the laboratory and calculated plasma osmolality. The osmolal gap is often used as a screen for toxic alcohol ingestion. The calculated plasma osmolality was 286 mOsm/kg of H_2O. The osmolal gap in our patient was 32 mOsm/kg of H_2O. The normal osmolal gap is 10–15 mmol/kg of H_2O and increases in the presence of low molecular weight substances. An osmolal gap of >25 mOsm/kg of H_2O suggests the presence of toxic alcohol but cannot identify the type of alcohol.[9]

Review of literature has suggested that the osmolal gap can be increased in patients with ethanol-induced acidosis without the presence of other alcohols,[10] presumably owing to the presence of acetone, which is produced by ethanol metabolism and by starvation.[11–13] The contribution of ethanol to the serum osmolality can be obtained by the formula "ethanol (mg/dL)/3.7,[8,14] which, in the present case, was 78/3.7 = 21.08 mOsm/kg of H_2O. The recalculated serum osmolality

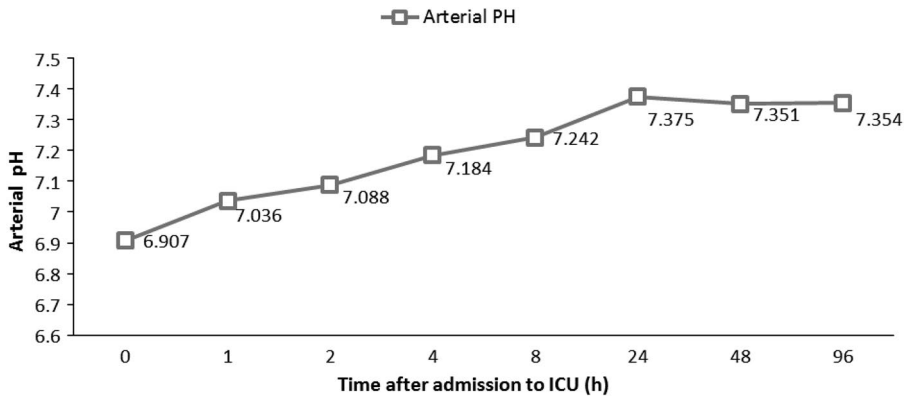

Figure 1: Time course of arterial pH values after admission to the intensive care unit (ICU).

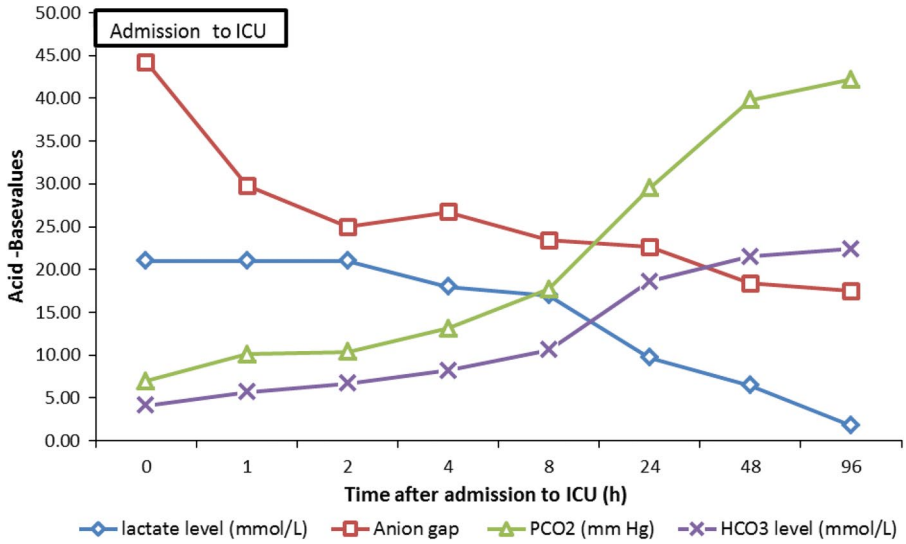

Figure 2: Time course of laboratory values of acid–base parameters for the first 12 h after admission to the ICU. Abbreviations: $PaCO_2$, partial pressure of carbon dioxide; HCO_3^-, sodium bicarbonate; ICU, intensive care unit.

Table 1: Serial arterial blood gas analysis (ABG) till discharge

ABG	0 h	1 h	2 h	4 h	8 h	24 h	48 h	96 h
pH	6.097	7.036	7.088	7.184	7.242	7.375	7.351	7.354
PCO_2 (mm HG)	7.0	10.1	10.4	13.1	17.7	29.5	39.8	42.2
PO_2 (mm HG)	131	135	139	75.8	106	80.4	80.2	78.4
HCO_3^- (mmol/L)	4.1	5.7	6.7	8.2	10.6	18.6	21.5	22.4
Lactate (mmol/L)	21	21	21	18	17	9.7	6.5	1.8
Na^+ (mmol/L)	128	124	121	122	122	130	133	134
K^+ (mmol/L)	4.3	4.5	4.7	3.9	4.0	3.2	2.9	3.4
Anion gap	44.2	29.8	25	26.7	23.4	22.6	18.4	17.5

would then be 286 + 21.1 = 307.1 mOsm/kg of H_2O. Thus, the osmolal gap now would be 11.1 mOsm/kg ,which is within the normal range and can be explained by ethanol consumption alone. Our patient vehemently denied intake of toxic alcohols, and, hence, his blood toxicology screen was not sent as these tests are not routinely available in our hospital.

Our patient did not show hypotension and hypoxia (SaO_2 on ambient air was 98%), factors responsible for type A lactic acidosis. In a case reported by Hulme ad Sherwood, severe lactic acidosis of 31 mmol/L was seen in a patient with alcohol-related generalized seizures.[9] Our patient did not experience seizures before admission. The question then arouse as to why this patient developed such severe lactic acidosis.

Ethanol is oxidized to acetaldehyde and then to acetate with the generation of two molecules of NADH: "Pyruvate, which is produced from metabolism of glucose and aminoacids, is metabolized to lactate, driven by the ratio of NADH to NAD^+. This path is the primary mechanism of alcohol metabolism in acute alcoholic intoxication, and drives the formation of large quantities of lactate. Lactate can only be metabolized in the presence of the enzyme pyruvate dehydrogenase (PDH)[10] Figure 3 back to pyruvate, which then enters the gluconeogenic pathway or enters the mitochondria to be metabolized to acetyl CoA by the enzyme pyruvate dehydrogenase (PDH)." Acetyl CoA then enters the Kreb's cycle to produce CO_2, water and 38 molecules of ATP. The enzyme PDH requires cofactor thiamine pyrophosphate. Thus, in case of thiamine deficiency, lactate cannot be metabolized to pyruvate and accumulates in large amounts resulting in severe lactic acidosis. Thus, lactate production is function of both pyruvate and NADH levels.[13] The presence of ethanol show an additive effect on lactate formation, over and above that caused owing to thiamine deficiency alone.[10]

It is not clear why certain individuals with alcohol dependency develop severe lactic acidosis, whereas others, such as those reported by Halperin et al.,[3] develop only mild acidosis. A review of the literature of alcohol-related lactic acidosis revealed only a few case reports in which arterial pH was <7.0.[2,15] The answer probably lies in thiamine deficiency, importance of which was first emphasized by Campell.[18] Thiamine deficiency, when present, makes a patient prone to life-threatening lactic acidosis. Our patient stayed alone and most of the times took alcohol, neglecting his diet and, therefore, was more likely to be in poor nutritional state and experience thiamine deficiency than an individual supported by family. Individuals with alcohol dependency have been found to experience multiple vitamin deficiencies, especially B vitamins. We, however, did not document his thiamine deficiency owing to the lack of this facility.

Approximately about 1,400 mmol of lactate is produced daily in the body of a 70-kg man, which is buffered by 1,400 mmol of HCO_3^- to sodium lactate. Under normal circumstances, liver takes up more than 60% of the lactate and converts it back to pyruvate in presence of the enzyme lactate dehyrogenase.[2] About 10% to 20% of the lactate is removed by the kidney. Our patient showed alcohol-related liver injury as evidenced by AST>ALT ratio of >1.5 and abnormal PT (INR), which too would have contributed to lactic acidosis owing to defective lactate metabolism in the liver.

In our patient, lactate levels alone could not account for the entirety of the anion gap. His initial serum glucose level was low excluding diabetic ketoacidosis as a cause of the anion-gap metabolic acidosis. As his blood lactate level (21 mmol/L) was less than Δ anion gap (30.2 mmol/L) and there was no history of toxic alcohol intake, in the presence of high urinary ketones, following a binge alcohol drinking, the only explanation was that this patient experienced associated AKA. Thus, our patient showed combined lactic and ketoacidosis, in which the primary element was lactic acidosis.

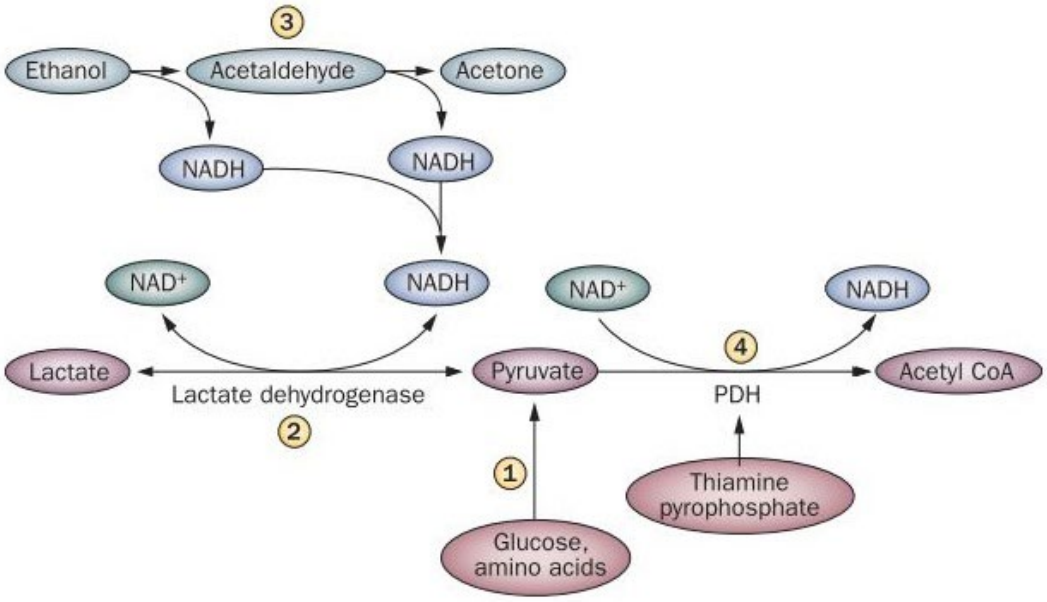

Figure 3: The metabolic pathways of ethanol and its role in lactate production.

In 1940, Dillion and his colleagues first described alcoholic ketoacidosis as a distinct entity.[2] It is characterized by an increased anion-gap metabolic acidosis with high serum ketone levels. It is typically found in patients after abrupt decrease in food and alcohol intake. Patients typically present with gastrointestinal symptoms such as abdominal pain, nausea and intractable vomiting and altered mental status.

Our patient had not eaten for 48 h before admission, had been drinking heavily, and was volume depleted initially, which set an ideal milieu for the development of alcoholic ketoacidosis.

Starvation causes the hepatic glycogen stores to deplete and ketogenesis to take place in the liver, decreased insulin sensitivity and increased production of counterregulatory hormones such as glucagon, cortisol, and epinephrine. They cause enhanced lipolysis, causing the release of free fatty acids to the liver, where they are preferentially converted into ketone bodies. Furthermore, prolonged vomiting causes dehydration, which in turn decreases renal perfusion and limits urinary excretion of ketoacids. In addition, volume depletion suppresses insulin release and increases concentration of counterregulatory hormones leading to viscous cycle. In addition, there is inhibition of gluconeogenesis by alcohol, resulting in hypoglycemia. Other acid-base disorders are also commonly found in this population.

Diagnosis may pose a problem owing to difficulty in detecting the ketone body. The usual method for detection of serum ketone is the nitroprusside test. This method is very sensitive for detection of acetoacetate but not sensitive for detection of beta hydroxy butyric acid, which is the main ketone body in AKA. The increased NADH:NAD ratio resulting from ethanol metabolism accentuates the enzymatic reaction from acetoacetate to hydroxybutyrate, explaining the acidosis seen with a negative serum nitroprusside reaction and strong urinary ketone positive reaction. We, however, could not measure beta hydroxybutyrate levels as this facility was not available in our hospital.

During the first 24 h of his hospital admission, his serum bicarbonate level rose to 18 mmol/L, accompanied by a rise in the serum pH. During this period, the urine ketone level remained high but the test for serum ketones, which was initially negative, became positive. There was an apparent worsening of the serum ketone level, while other measurements suggested that the patient's condition was improving. This could be explained by the conversion of beta hydroxybutyrate back to acetoacetate, as a predominance of NAD^+ drove the reaction in the opposite direction during treatment. Because acetoacetate is the substance primarily measured in the nitroprusside reaction, the increasingly higher serum ketone levels do not reflect worsening of the metabolic condition but rather the conversion of the ketones to a form that is now measured by the laboratory test.

Seven episodes of severe alcoholic ketoacidosis following an alcohol binge in chronic alcohol abusers are described in literature in six nondiabetic female patients, including one pregnant lady who developed two episodes.[16] Their mean pH was 7.25 and mean anion gap 18. All were treated with dextrose normal saline and small amount of bicarbonate and they improved with treatment.

Using Winter's formula for calculating CO_2 compensation in metabolic acidosis ($PCO_2 = 1.5 \times HCO_3 + 8 \pm 2$), predicted PCO_2 ranged between 12.2 and 16.2, which is higher than CO_2 level of 7 mm Hg observed in our patient. This suggested the presence of respiratory alkalosis. At the same time, the ratio of Δ anion gap to Δ HCO_3 was > 1, which suggested the presence of metabolic alkalosis caused by repeated vomiting. Thus, our patient showed "triple" acid-base disorder. It is present in about 10% of cases of AKA.[17]

Management

Treatment of lactic acidosis involves identification and treatment of the underlying cause. Treatment includes restoration of intravenous fluid volume, supplemental oxygen, improving cardiac output with fluids and inotropes, and management of sepsis. The use of sodium bicarbonate for the treatment of lactic acidosis is recommended but is also widely criticized. The arguments against its use are that such a therapy causes hypercapnia and exerts negative effect on intracellular pH (causing it to become more acidotic paradoxically), it does not improve cardiovascular parameters, it may decrease the ionized calcium levels, and there is no improvement in the outcome of the patients treated with bicarbonate. However, such therapy may possibly "buy time" while the underlying cause of acidosis is determined and treated. Dichloroacetate, although decreased the lactate concentration, showed no beneficial effects on the outcome.

In case of severe lactic acidosis in alcohol-dependent patients, such as in this case, it is important to consider the possibility of underlying thiamine deficiency. In this situation, intravenous thiamine must be must be supplemented as early as possible, as it helps in the reversal of acidosis. Hemodialysis should be considered in life-threatening cases.[10] Alcohol-related ketoacidosis responds rapidly to intravenous fluids with glucose and normal saline and are indicated except in patients with cardiac failure where fluid administration requires careful monitoring and in patients with hyperglycemia where close monitoring of glucose levels is required.[10] The outcome of such patients with alcohol-related lactic acidosis is excellent with early intervention.

Conclusion

To conclude, our patient presented with severe, life-threatening anion-gap metabolic acidosis, probably as a result of severe lactic acidosis caused by acute alcohol binge coupled with thiamine deficiency. The anion gap was also partly contributed by AKA. Patient responded well to intravenous fluids, thiamine administration, and one bicarbonate hemodialysis and was discharged in stable condition. Prompt recognition of the abnormalities and stepwise assessment of the laboratory parameters by physician are crucial for developing an appropriate management plan for reversal of this condition.

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