Toluene Toxicity as a Cause of Elevated Anion Gap Metabolic Acidosis

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Introduction

Dyspnea and elevated anion gap metabolic acidosis are common presenting problems in critically ill patients. In certain cases, however, the standard workup for these problems does not reveal an etiology, and other diagnoses must be considered. We describe a woman who presented with dyspnea and severe acidemia due to a profound metabolic acidosis, who was subsequently found to have toluene toxicity secondary to inhalant abuse. This case demonstrates that when the initial workup for an elevated serum anion gap acidosis is unrevealing, alternative etiologies such as inhalant abuse should be suspected and evaluated.

Case Summary

A 47-year-old woman presented to the emergency department complaining of a one-day history of dyspnea. She had been evaluated at another hospital the previous day for right hip pain sustained in a mechanical ground-level fall. No orthopedic intervention was required after imaging revealed an old right hip fracture. The patient was discharged to home with oral analgesics. The following morning she awoke with dyspnea that did not improve with inhaled bronchodilators. She denied associated chest pain, fever, chills, or cough, but did report headache, decreased oral intake, and low urine output.

The patient had a history of asthma, controlled with inhaled fluticasone and albuterol, with no history of intubation for respiratory failure. She denied any symptoms suggestive of a recent exacerbation. She had a remote history of tuberculosis, for which she completed 6 months of directly observed therapy. She had chronic hypokalemia and proteinuria secondary to biopsy-confirmed mesangio-proliferative glomerulonephritis, but her serum creatinine had remained within normal limits. She had a chronic distal renal tubular acidosis, which her nephrologist attributed to chronic toluene toxicity secondary to spray paint inhalation. Her social history was noteworthy for inhalant abuse (spray paint and paint thinner inhalation), although she denied any recent use of this substance. She was a non-smoker and denied recent use of alcohol or other illicit drugs.

In the emergency department the patient was afebrile, with a blood pressure of 120/99 mm Hg, heart rate of 93 beats/min, respiratory rate of 20 breaths/min, and an oxygen saturation of 99% on room air. She was tachypneic but was talking in complete sentences, without evidence of respiratory distress or accessory muscle use. She had clear breath sounds bilaterally, without crackles or wheezes. On cardiac examination she had no murmur, a normal pulmonic component of the second heart sound, no right ventricular heave, and no evidence of elevated neck veins. Her right hip was tender to palpation but had intact range of motion. There was no lower-extremity edema.

Basic laboratory studies revealed: blood urea nitrogen 25 mg/dL, creatinine 4.2 mg/dL (baseline 0.9 mg/dL), sodium 132 mEq/L, potassium 5.1 mEq/L, chloride 110 mEq/L, and an unmeasurably low serum bicarbonate (< 5 mEq/L). The anion gap could not be calculated but was at least 18. Serum osmolality was 299 mOsm/kg. An arterial blood gas obtained while the patient was receiving an unspecified amount of supplemental oxygen via nasal cannula revealed a pH of 6.95, a PaCO2 of 9 mm Hg, and a PaO2 of 165 mm Hg. The complete blood count revealed a white-blood-cell count of 19×10^9/L, hematocrit 39%, and platelet count of 325×10^9/L. Serum lactate was 2.1 mmol/L. Urinalysis demonstrated a pH of 6.0, 2+ protein, 1+ red blood cells, and trace glucose and ketones. The urine anion gap was 84. A chest radiograph revealed no opacities, effusion, or pneumothorax. A urine toxicology screen was negative, and a blood alcohol panel was negative for ethylene glycol or ethyl, methyl, and isopro-
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The patient was admitted to the intensive care unit, where her metabolic acidosis was treated with a sodium bicarbonate drip. Over the following days she received approximately 5 L of isotonic sodium bicarbonate solution, and was subsequently switched to scheduled oral bicarbonate. A room-air arterial blood gas performed on the second day of admission demonstrated a pH of 7.25, a $P_{aCO_2}$ of 24 mm Hg, and a $P_{aO_2}$ of 115 mm Hg. During her admission the patient’s serum bicarbonate rose to 23 mEq/L and her serum creatinine decreased to 1.1 mEq/dL. Her anion gap, which had peaked at 22, decreased to 10 within 2 days of admission. She developed persistent hypokalemia and received aggressive electrolyte replacement. Her dyspnea improved with resolution of her acidemia. She was transferred to the medicine ward on hospital day 2, and discharged to home on hospital day 5.

Discussion

This patient presented with a severe form of a common abnormality in the intensive care unit and was subsequently found to have a less common etiology of this problem: toluene toxicity.

This patient’s initial diagnostic evaluation revealed a profound metabolic acidosis, with an elevated serum anion gap. Her arterial blood gas revealed an extreme acidemia (pH = 6.95) despite an impressive compensatory respiratory alkalosis ($P_{aCO_2}$ 9 mm Hg) that was greater than that of climbers near the summit of Mount Everest¹ and close to that of the lowest known reported human $P_{aCO_2}$ (6 mm Hg in a 12-year-old girl with diabetic ketoacidosis).² Even though this patient had dyspnea, a severe acidosis and a very low pH, she was not intubated, as she had intact gas exchange and no evidence of respiratory muscle fatigue. In fact, a reflexive decision to intubate this patient based on her serum pH and respiratory rate might have proven catastrophic. When patients hyperventilate to this degree, it is difficult to match their intrinsic ventilatory efforts through mechanical ventilation. Failure to match the patient’s pre-intubation spontaneous minute ventilation would lead to a rise in the $P_{aCO_2}$ and a further decrease in the serum pH.

Although her initial serum bicarbonate was undetectable in our laboratory, through the use of the Henderson-Hasselbach equation we calculated a value of approximately 2 mEq/L. This profound acidosis was associated with an elevated anion gap of approximately 18; further analysis revealed that she had a concomitant non-anion-gap metabolic acidosis.

The causes of metabolic acidosis associated with an elevated serum anion gap are listed in Table 1.³,⁴ The patient’s initial workup, however, failed to find evidence of any of the more common processes. She did have an elevated lactate and blood urea nitrogen, but neither value was high enough to explain her degree of acidosis. A blood alcohol panel was entirely negative, and although trace ketones were noted in the urinalysis, there was little evidence in the history or laboratory data to suggest alcoholic, diabetic, or starvation ketoacidosis. When the common differential for her presenting problems was exhausted, a secondary survey of her social history revealed evidence in the history or laboratory data to suggest alco-

Table 1. Causes of Elevated Anion Gap Metabolic Acidosis

<table>
<thead>
<tr>
<th>Acidosis</th>
<th>Causes</th>
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</thead>
<tbody>
<tr>
<td>Ketoacidosis</td>
<td>Alcohol, Diabetic, Starvation</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Cyanide poisoning, Carbon monoxide poisoning, D-lactic acidosis</td>
</tr>
<tr>
<td>Cyanotic acidosis</td>
<td>Ketoacidosis (jejuno-ileal bypass, small bowel resection, short bowel syndrome)</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td>Excess inhaled β agonists, Exercise above the anaerobic/ventilatory threshold, Hereditary disorders (glucose-6-phosphatase deficiency, fructose-1,6-phosphatase deficiency), Medications (iron, isoniazid, metformin, zidovudine), Seizures, Severe hypoxemia, Shivering, Shock (sepsis, hypovolemia, cardiogenic), Massive rhabdomyolysis</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Toxins metabolized to acids, Ethylene glycol (oxalic acid), Methanol (formic acid), Paraldehyde (acetic and chloroacetic acid), Salicylates, Toluene (hippuric acid)</td>
</tr>
</tbody>
</table>

Toluene is an aromatic hydrocarbon that is often used as a solvent in paints, paint thinners, glues, and disinfectants. It is the intoxicating element of many inhalants, which may be consumed by sniffing, snorting, bagging (inhaling from a plastic bag into which the substance has been sprayed), and huffing (inhaling through a cloth that has been saturated with the substance). The use of inhalants, such as toluene, is the second most common form of substance abuse among teenagers. The prevalence of use peaks during adolescence and decreases in adulthood. Inhalant use is uncommon among African Americans but disproportionately prevalent among Hispanics, non-Hispanic whites, and Native Americans. It is more common among men than women.⁵
Acute toluene exposure can provoke disorientation, euphoria, exhilaration, and tinnitus. Higher levels cause disinhibition, decreased level of consciousness, hallucinations, nausea, and fatigue. A hydrophobic compound, it accumulates in lipids with chronic use. As a result, the intoxicating effects may persist for hours after cessation of use, due to deposition in body fat stores. Toluene intoxication can lead to a metabolic acidosis via 2 mechanisms. First, it is metabolized to hippuric acid by way of benzoic acid, both of which are found in the serum of patients who abuse toluene. Neither benzoic acid nor hippuric acid production is impaired or hippuric acid accumulation in lipids with chronic use. As a result, the intoxicating effects may persist for hours after cessation of use, due to deposition in body fat stores. Toluene intoxication may also lead to a normal anion gap acidosis by impairing renal elimination of ammonium ion, the primary carrier for excess hydrogen ions. Given that ammonium is the primary unmeasured cation in urine, our patient’s elevated urine anion gap suggests that ammonium ion excretion was, in fact, impaired. In addition, her elevated urine pH (6.0) was also inappropriately high for her degree of acidosis, providing further evidence of this pathology.

The treatment of toluene toxicity is conservative management while the kidneys excrete excess hippuric acid, recover from the distal renal tubular acidosis, and restore the body’s acid-base balance. Sodium bicarbonate is administered intravenously and orally to correct life-threatening acidemia, and electrolyte abnormalities, such as hypokalemia and hypophosphatemia, should be rectified by supplementation. Hypervolemia and associated pre-renal kidney injury should be treated with isotonic crystalloid. In severe cases, especially when renal function cannot be recovered, hemodialysis may be needed to correct acidemia and electrolyte derangements and eliminate toluene metabolites. Unlike some other intoxications, such as salicylate poisoning, specific dialysis indications have not been delineated. Because toluene accumulates in the body’s fat stores, complete body clearance may take several days, even with intact renal function.

Toluene is just one of several volatile agents that are abused in this manner and have the potential to cause serious toxicity. Other common agents include benzene and chlorohydrocarbons, which, like toluene, are found in countless over-the-counter products such as gasoline, paint thinner, and spray paint. The intoxicating effects of other volatile compounds are similar in character, onset, and duration to that of toluene. Because of the diversity of compounds found in inhalants it is often difficult to attribute specific sequelae to individual offending agents. In addition to the above-described renal sequelae, inhalant abuse can cause reversible hepatotoxicity and potentially lethal cardiac dysrhythmias. Various neuropsychiatric disorders can also result from chronic abuse, and chronic abusers may exhibit deficits in memory, attention, and visual-motor function. Both tolerance and withdrawal can occur with any of these agents. Deaths associated with inhalant abuse are commonly due to trauma and asphyxiation, though the specific mechanism of death is often uncertain.

Inhalant abuse is a common, yet under-recognized, form of substance abuse, especially among the adolescent population. Given the prevalence of this problem, it should be considered in the differential diagnosis of metabolic derangements when no other clear etiologies are identified in the initial evaluation.

REFERENCES