Metabolic acidosis in toluene sniffing

Jon Tuchscherer, MD*; Habib Rehman†

ABSTRACT

Toluene sniffing, frequently described under the generic category of ''glue sniffing,'' is a potential cause of normal anion gap metabolic acidosis due to distal renal tubular acidosis. Urine anion gap is used to diagnose metabolic acidosis of a normal anion gap variety; however, pitfalls exist when using urine anion gap in the setting of toluene sniffing. We present the case of a young woman who had a normal anion gap metabolic acidosis due to toluene sniffing and an unexpectedly low urine anion gap. In such a scenario, the urine anion gap will underestimate the rate of ammonia excretion when the conjugate bases of acids other than HCl are excreted in large quantities. Estimation of the urine osmolal gap will provide a more accurate ammonia excretion rate in these circumstances. The challenges in interpretation of the urine anion gap and ammonia excretion in the setting of distal renal tubular acidosis due to toluene toxicity are discussed.

RÉSUMÉ

L'inhalation de toluène, souvent incluse dans la catégorie générale d'« inhalation de vapeurs de colle » est une cause possible d'acidose métabolique à trou anionique normal par acidose tubulaire rénale distale. L'analyse du trou anionique urinaire sert à diagnostiquer l'acidose métabolique dans divers états pathologiques à trou anionique normal, mais l'analyse du trou anionique urinaire pose un problème dans le contexte de l'inhalation de toluène. Il sera question ici du cas d'une jeune femme qui avait une acidose métabolique à trou anionique normal, consécutif à l'inhalation de toluène, mais chez qui le trou anionique urinaire était particulièrement faible. Dans ce contexte, l'analyse du trou anionique urinaire se traduit par une sous-estimation du taux d'excrétion d'ammoniac, tandis que les bases conjuguées d'acides autres que l'HCl sont excrétées en grande quantité; alors, l'estimation du trou osmolaire urinaire fournira une évaluation plus précise du taux d'excrétion d'ammoniac. Les difficultés d'interprétation du trou anionique urinaire et de l'excrétion d'ammoniac dans le contexte d'une acidose tubulaire rénale distale due à la toxicité du toluène feront l'objet de discussion.

Keywords: anion gap, glue sniffing, metabolic acidosis, osmolal gap, toluene

Toluene sniffing, frequently described under the generic category of ''glue sniffing,'' is a potential cause of normal anion gap metabolic acidosis due to distal renal tubular acidosis. Urine anion gap is used in the diagnosis of distal renal tubular acidosis to estimate urinary ammonia excretion. A low or negative urine anion gap indicates high ammonia (NH_4^+) excretion and thus an appropriate response to systemic acidosis. Urine NH_4^+ excretion should be higher in patients with acidosis unless there is a defect in urine hydrogen ion excretion, that is, distal renal tubular acidosis. Urine anion gap, however, will underestimate the rate of NH_4^+ excretion when the conjugate bases of acids other than HCl are excreted in large quantities, such as in the setting of toluene toxicity. We present the case of a young woman who had a normal anion gap metabolic acidosis due to toluene sniffing and an unexpectedly low urine anion gap and discuss the challenges in interpretation of the urine anion gap and ammonia excretion in the setting of distal renal tubular acidosis due to toluene toxicity.

CASE REPORT

A 38-year-old woman presented to the emergency department (ED) with a 24-hour history of pleuritic, left-sided chest pain, a nonproductive cough, and shortness of breath on exertion. She had a history of hypertension, heavy alcohol use, smoking, and gastroesophageal reflux disease. Three months prior to her ED presentation, she was hospitalized following an acetaminophen overdose, and 2 months following that, she was rehospitalized with alcoholic hepatitis. Her

From the *Department of Medicine, University of Saskatchewan, Regina, SK, and †Department of Medicine, Regina General Hospital, Regina, SK.

Correspondence to: Dr. Habib Rehman, Department of Medicine, Regina Qu'Appelle Health Region, Regina General Hospital, 1440 – 14th Avenue, Regina, SK S4P 0W5; habib31@sasktel.net.

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only medications were lisinopril and omeprazole. She stated that she had last consumed alcohol, approximately 6 ounces of a wine cooler, 24 hours previously and had been "huffing" (sniffing) varnish 1 day prior to presentation.

On physical examination, the patient was awake, with a temperature of 36.8°C (98.2°F), heart rate of 94 beats/minute, blood pressure of 113/43 mm Hg, and respiratory rate of 16 breaths/minute. Chest auscultation revealed decreased air entry to the base of the left lung and scant bibasilar crackles. Mild right upper quadrant abdominal discomfort was elicited on palpation. The rest of the physical examination was unremarkable.

Laboratory investigations revealed the following: white blood cell count 8.1 $\times$ 10^9/L (4.0–10.0 10^9/L), albumin 25 g/L (35–50 g/L), sodium 144 mmol/L (135–145 mmol/L), chloride 122 mmol/L (98–110 mmol/L), CO_2 14 mmol/L (21–30 mmol/L), urea 1.5 mmol/L (3.0–7.1 mmol/L), glucose 5.7 mmol/L (3.6–11.0 mmol/L), potassium 2.9 mmol/L (3.5–5.0 mmol/L), anion gap 14 mmol/L (9–15 mmol/L), and serum osmolality 292 mmol/kg (280–305 mmol/kg). Urine chemistry results on a spot sample were pH 7.5 (5–8), sodium 44 mmol/L, potassium 15.2 mmol/L, chloride 95 mmol/L, and urea 22.0 mmol/L. The urine osmolality was 249 mmol/kg (300–900 mmol/kg).

A urine toxicology screen was negative. Blood alcohol and acetaminophen levels were normal. An electrocardiogram revealed no abnormalities, and a chest radiograph was unremarkable. Arterial blood gases measurement on room air revealed the following: pH 7.27, carbon dioxide partial pressure (pCO_2) 28 mm Hg, oxygen partial pressure (pO_2) 103 mm Hg, HCO_3^- 14 mmol/L, and oxygen saturation 98%. Because of the 24-hour history of pleuritic chest pain, ventilation/perfusion lung scanning was done and showed no evidence of a pulmonary embolism.

The diagnosis of hyperchloremic hypokalemic metabolic acidosis of normal anion gap variety due to distal renal tubular acidosis caused by toluene was made. In consultation with the regional poison control centre, the patient was admitted to hospital and treated with supplemental oxygen and intravenous normal saline and potassium chloride. She responded well, and her dyspnea and chest pain resolved by her third day of admission, although her hypokalemia persisted. The patient was discharged home on oral potassium (KCl 20 mEq three times daily) and sodium bicarbonate (500 mg three times daily). She was seen in follow-up 4 weeks after discharge and was doing well.

DISCUSSION

Inhalant abuse is common, particularly in socioeconomically disadvantaged areas of North America. An estimated 22.5 million people in the United States have used an inhalant for its psychoactive properties at least once.[1] Glue, shoe polish, toluene, spray paints, gasoline, and lighter fluid are commonly abused inhalants. Acute effects of inhalant intoxication include dizziness, ataxia, slurred speech, salivation, flushing, euphoria, lethargy, motor retardation, tremor, blurred vision, muscle weakness, depressed reflexes, nystagmus, stupor, and coma. Long-term effects include myocardial damage, pulmonary toxicity, hepatic toxicity, and cognitive and memory problems. Renal toxicity can manifest as high anion gap metabolic acidosis, renal tubular acidosis, Fanconi syndrome, urinary calculi, glomerulonephritis, and Goodpasture syndrome.[2] An understanding of the assessment of metabolic acidosis in the setting of inhalant abuse is essential to its proper management.

Metabolic acidosis is characterized by a primary reduction in serum bicarbonate (HCO_3^-) concentration, a secondary decrease in the arterial pressure of carbon dioxide ($PaCO_2$), and a reduction in blood pH. Acute metabolic acidosis usually results from overproduction of organic acids such as ketoacids and lactic acid. Chronic metabolic acidosis is most often due to bicarbonate wasting or impaired renal acidification.

The determination of anion gap facilitates the classification of metabolic acidosis as high or normal anion gap metabolic acidosis, thus narrowing the differential diagnosis. Anion gap is increased in the presence of excess amounts of inorganic acids (e.g., phosphate, sulphate), organic acids (e.g., ketoacids, lactate), or exogenous acids (e.g., salicylates) that are incompletely neutralized by bicarbonate. The primary causes of elevated anion gap metabolic acidosis are uremia, lactic acidosis, ketones, or toxin ingestion (e.g., ethanol, methanol, ethylene glycol, propylene glycol, and salicylates). A classic mnemonic for the causes of elevated anion gap metabolic acidosis is "MUDPILES" (methanol, uremia, diabetic ketoacidosis, propylene glycol, isoniazid or iron, lactic acidosis, ethylene glycol, salicylates).

Normal anion gap metabolic acidosis is caused by excessive loss of HCO_3^- or an inability to excrete H^+.

Hyperchloremia is typical in normal anion gap metabolic acidosis. Given that urine ammonia concentration is generally not measured in most laboratories, urine anion gap and urine osmolal gaps are used as surrogate markers of ammonia excretion in patients with hyperchloremic metabolic acidosis. A negative urine anion gap suggests HCO_3^- loss from the gastrointestinal tract; a positive urine anion gap suggests an inability to excrete H^+ from the kidneys.[3] A significant difference between the measured and the calculated urine osmolality is the most reliable test to assess the rate of urinary excretion of NH_4^+. Gastrointestinal losses, renal tubular acidosis, and ureteric diversion procedures are the most common causes of normal anion gap metabolic acidosis. A useful mnemonic for the causes of hyperchloremic normal anion gap metabolic acidosis is "HARDUP": hyperalimentation, acetazolamide, renal tubular acidosis, diarrhea, ureterostomy, and pancreatic fistula.[4]

In our patient, the urine pH was inappropriately high in the presence of systemic acidosis, indicating a defect in the urinary hydrogen ion excretion. However, urine pH may be misleading in differentiating renal from nonrenal causes of hyperchloremic metabolic acidosis because it measures only free hydrogen ions in the urine, whereas free hydrogen ions contribute only a small proportion of total urinary hydrogen excretion.[5] Urinary NH_4^+ excretion provides a more robust evaluation of hydrogen ion excretion and thus urinary acidification. Given that most laboratories do not test urine NH_4^+, urine anion gap is a clinically useful surrogate measure of urine NH_4^+ excretion in patients with disorders of urine acidification. A low or negative urine anion gap suggests high NH_4^+ excretion and thus an appropriate response to systemic acidosis. Urine NH_4^+ excretion should be higher in patients with acidosis except in cases where there is a defect in urine hydrogen ion excretion (i.e., distal renal tubular acidosis).

The urine anion gap in our patient was −35.8 (calculated by urine Na^+ + urine K^+ − urine Cl^-). This was contrary to our expectations in a case of distal renal tubular acidosis, where a high urine anion gap would have been expected due to the inability of the kidneys to excrete excess hydrogen ions. The calculation of the urine anion gap does not accurately estimate the rate of excretion of NH_4^+ when large amounts of unmeasured anions are present in the urine. The urine anion gap will underestimate the rate of NH_4^+ excretion when the conjugate base of acids other than HCl are excreted in large quantities, such as in diabetic ketoacidosis, salicylate poisoning, and toluene toxicity.[6]

Measurement of the urine osmolal gap is useful in estimating urine NH_4^+ in patients in whom NH_4^+ is being excreted in conjugation with β-hydroxybutyrate, salicylate, sulphate, or hippurate.[7] The urine osmolal gap in our patient was 108.6 (calculated by measured osmolality − calculated osmolality: 249 − 140.4). Urine osmolality is calculated by the formula $2(Na^+ + K^+)$ + urea + glucose. NH_4^+ accounts for much of this osmolal gap and therefore suggests a high rate of NH_4^+ excretion in the absence of other osmolytes. Hippurate, a metabolite of toluene, would account for the rest of the osmolal gap.[8]

Toluene is an aromatic hydrocarbon found in glues, paint, paint thinners, cements, and solvents. Toluene toxicity may be caused by industrial exposure, abuse from inhalation, or ingestion. Toluene is metabolized to hippuric acid via benzoic acid, and toluene sniffing is associated with hyperchloremic normal anion gap metabolic acidosis. Hippurate is excreted through the kidneys along with a cation such as NH_4^+, Na, or K. This increased rate of excretion of organic anions in association with hippurate is responsible for underestimation of the urine anion gap, giving a false-positive result for NH_4^+ excretion. In addition to distal renal tubular acidosis, toluene toxicity has also been associated with proximal renal tubular defect as well as high anion gap metabolic acidosis due to accumulation of hippuric acid during a period of low glomerular filtration, for example, due to vomiting-induced volume depletion.[9]

CONCLUSION

In the setting of inhalant toxicity from toluene, arterial blood gases and electrolyte measurement will confirm the presence of metabolic acidosis. Serum anion gap calculation will narrow the differential diagnosis to normal or high anion gap metabolic acidosis. Urine anion gap must also be calculated in normal anion gap metabolic acidosis to assess the renal response to acidosis. The urine anion gap will, however, underestimate the rate of NH_4^+ excretion when the conjugate bases of acids other than HCl are excreted in large quantities. Estimation of the urine osmolal gap in these circumstances provides a more accurate ammonia excretion rate.

Competing interests: None declared.

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