Aniline and methanol toxicity after shoe dye ingestion.

Kenneth D. Katz MD
Lehigh Valley Health Network, kenneth_d.katz@lvhn.org

Anne-Michelle Ruha

Steven C Curry

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ANILINE AND METHANOL TOXICITY AFTER SHOE DYE INGESTION

Kenneth D. Katz, MD,*† Anne-Michelle Ruha, MD,*†§ and Steven C. Curry, MD*†‡

*Department of Medical Toxicology, Banner Good Samaritan Medical Center, †Department of Emergency Medicine, Maricopa Medical Center, §Department of Clinical Medicine, University of Arizona College of Medicine, and ‡Department of Emergency Medicine, University of Arizona College of Medicine, Phoenix, Arizona

□ Abstract—A 39-year-old woman intentionally ingested Amberes™ shoe dye containing both methanol and aniline. She subsequently developed life-threatening methanol poisoning, methemoglobinemia, hemolytic anemia, and sulfhemoglobinemia. Treatment involved methylene blue infusion, emergent hemodialysis, fomepizole therapy, and blood products. Multiple toxicities can occur after ingestion of shoe dyes. © 2004 Elsevier Inc.

□ Keywords—aniline; methanol; shoe dye; methemoglobinemia; sulfhemoglobinemia; hemolytic anemia

INTRODUCTION

Emergency physicians often encounter patients who ingest non-food products with the intent of harming themselves. Information provided either on the product label or from the poison center database is usually helpful in determining the contents of a particular product and, therefore, the potential clinical effects after ingestion. We present a case of ingestion of a Mexican shoe dye, which stated only 'contiene metanol' on the packaging. Information regarding the specific product contents could not be obtained through standard poison center databases. In addition to the initially anticipated methanol toxicity, the patient subsequently developed severe methemoglobinemia, sulfhemoglobinemia, and hemolytic anemia from aniline contained in the shoe dye.

CASE REPORT

A previously healthy 39-year-old woman presented to the Emergency Department (ED) 30 min after intentionally ingesting 125 mL of Amberes™ Mexican shoe dye in a suicide attempt. She was given 50 g of activated charcoal during transport to the ED. In the ED, she offered no physical complaints, and her initial vital signs were normal with the exception of a room air pulse oximetry of 90%. Administration of 2 L oxygen via nasal cannula had no effect on the oximetry reading. The patient was alert and oriented with a depressed affect, answering questions appropriately. The physical examination was remarkable only for blue dye staining the lips. She was in no apparent respiratory distress and the lungs were clear. Initial laboratory studies obtained 1 h after the ingestion, including complete blood count (CBC) and complete metabolic panel (CMP) were normal except for a serum glucose (GLU) of 267 mg/dL (65–109), an alanine aminotransferase (ALT) of 65 U/L (2–31), a CO_2 of 17 mmol/L (22–30) and glucosuria. Anion gap was 19. Aspartate aminotransferase (AST) was 39 U/L (10–41) and prothrombin time (PT) was not obtained. Salicylate level, acetaminophen level, ethanol level, urine Enzyme Multiple Immunoassay Test (EMIT) screen for drugs of abuse and urine human choriogonadotropin (HCG) were all negative, and the electrocardiogram was normal. Serum methanol and ethylene glycol levels and serum osmolality were sent to a neighboring facility. An

arterial blood gas (ABG) on 45% FIO_2 demonstrated a pH of 7.42 (7.36–7.44), a PCO_2 of 29 mm Hg (36–44), a PO_2 of 154 mm Hg (76–100), a bicarbonate of 18 mmol/L (23–38) and a base excess of −4.9 mmol/L (−2.5 −2.5). Co-oximetry revealed a methemoglobin level of 43%, but was unrecognized by the Emergency Department staff. The patient was observed in the ED and treated with i.v. fluids while awaiting further laboratory results. She continued to be without complaints or apparent distress until 4 h after initial presentation, when she suddenly became unresponsive without respiratory effort, requiring emergency endotracheal intubation. Her clinical deterioration was presumed secondary to methanol, and at this time she was placed on an ethanol drip and transferred to our toxicology treatment center.

Upon arrival, the patient exhibited an extraordinarily dusky appearance despite mechanical ventilation, and had been sedated and relaxed with vecuronium for transport. Her vital signs were blood pressure 100/70 mm Hg, pulse 75 beats/min, respiration 12 breaths/min, and pulse oximetry 88% on FIO_2 100%. The remainder of the physical examination, including funduscopy, was unremarkable except that coma persisted after neuromuscular blockade had resolved. The patient was given a loading dose of fomepizole (15 mg/kg), arrangements were made for emergent hemodialysis, and repeat laboratory studies were obtained. Concurrently, an ABG with co-oximetry was obtained on 100% FIO_2 and demonstrated: pH 7.37, pCO_2 21, pO_2 366, HCO_3 12, a carboxyhemoglobin 0.0%, an oxyhemoglobin 25.6%, and a methemoglobin fraction of 72.4%. Methylene blue was administered intravenously at a dose of 2 mg/kg, and a repeat methemoglobin fraction approximately 1 h after treatment was 25.9%. Blood and serum laboratory values obtained 7 h after the ingestion included: white blood count (WBC) 16.0 K/mm^3 (4–11), hemoglobin (HGB) 14.4 g/dL (11.5–16), platelet (PLT) 214 K/mm^3(130–450), rare red blood cell (RBC) fragments, PT 16.2 s (11.5–13.4), glucose 149 mg/dL, blood urea nitrogen (BUN) 9 mg/dL, creatinine 0.6 mg/dL, Na^+ 141 mmol/L, K^+ 7.9 mmol/L, Cl^- 112 mol/L, CO_2 13 mmol/L, AST 139 IU/L (10–41), ALT 95 IU/L, and methanol 89 mg/dL.

The patient received four doses of fomepizole and 6 h of hemodialysis, resulting in a methanol level of 10 mg/dL. She developed recurrent methemoglobinemia, requiring repeated doses of methylene blue and was eventually placed on a continuous infusion at 0.1 mg/kg/h. The infusion was discontinued on hospital day three, when her methemoglobin fraction eventually reached 0% and remained undetectable. The patient's clinical condition gradually improved over the next several days, and she was extubated. A gradual decline in HGB to 7.7 g/dL was noted, with RBC fragments and spherocytes present on peripheral smear. On hospital day

four, two units of packed red cells were transfused. At this time the ABG and co-oximetry studies remained normal. After receiving a total of four units packed red cells the patient's hemoglobin remained stable at 8.9 g/dL. A sulfhemoglobin fraction of 5.1% was measured on hospital day seven. She was discharged in good condition on hospital day nine after psychiatric interview. Gas chromatography/mass spectroscopy (GC/MS) analysis of the dye confirmed the presence of aniline, and urine GC/MS detected aniline along with acetanilide and acetaminophen, known metabolites of aniline.

DISCUSSION

Methanol and aniline are found in several commercial products and can independently cause toxicity. Methanol, known as wood alcohol, is a clear, colorless liquid used mainly as a solvent in many products, including stains, dyes, adhesives, thinners, antifreeze products and cleaning solutions. Methanol is rapidly absorbed from the gastrointestinal tract with peak concentrations reached within 30 to 60 min. Methanol itself possesses relatively low toxicity, with toxic effects due to metabolism via alcohol dehydrogenase to formaldehyde and then to formic acid (1). Methanol poisoning is characterized, in part, by coma, pancreatitis, blindness and metabolic acidosis. Treatment entails administration of an inhibitor of alcohol dehydrogenase, hemodialysis and folinic acid (1).

Aniline is an aromatic amine used in the production of rubber products, dyes, pesticides and pigments (2). Aniline's acute toxicity is attributed to the oxidizing action of its metabolite phenylhydroxylamine, resulting in methemoglobinemia, sulfhemoglobinemia and hemolysis (3). Methemoglobin can be formed from exposure to an oxidizing agent, but can stem from idiopathic, genetic or dietary causes as well. Methemoglobinemia involves oxidation of ferrous (Fe^{+2}) to ferric (Fe^{+3}) iron within hemoglobin, shifting the oxygen-hemoglobin dissociation curve to the left. Thus, transport and delivery of oxygen is impaired, resulting in tissue hypoxemia (4). Clinical manifestations of methemoglobinemia may include cyanosis, headache, dizziness, dyspnea, tachypnea, tachycardia, coma, seizures, and death (4).

Sulfhemoglobinemia is often caused by similar toxins that form methemoglobin and involves binding of a sulfur molecule to a heme moiety. This results in a shift of the oxygen-hemoglobin dissociation curve to the right, which enhances oxygen tissue delivery, limiting severe toxicity. Clinical manifestations may include cyanosis, as well as those engendered from concomitant methemoglobinemia and hemolysis. Sulfhemoglobinemia does not respond to methylene blue (4,5).

Hemolytic anemia may accompany methemoglobinemia and sulfhemoglobinemia due to overwhelming red blood cell oxidant stress (4). Diagnostic clues include declines in hemoglobin concentration and the presence of spherocytes and fragmented erythrocytes (including bite cells) on peripheral smear. Specialized staining of blood may reveal Heinz bodies, but was not performed in this case (6).

On initial presentation, our patient demonstrated an anion gap metabolic acidosis ($[Na^+] - [Cl^- + CO_2] = 143 - [107 + 17] = 19$), but lacked central nervous system (CNS) or ocular symptoms that can occur with methanol poisoning. The lack of CNS and ocular symptoms was likely due to the early presentation, because methanol must undergo metabolism to formate to generate toxicity. Although methanol itself may produce inebriation, it does not consistently do so, and patients often present after methanol ingestion with a normal neurological examination. Furthermore, it is doubtful that methanol toxicity alone was responsible for her sudden clinical deterioration 4 h after presenting to the ED. The sudden loss of consciousness and apnea were more likely related to inadequate oxygen delivery to tissues due to methemoglobinemia.

Our patient demonstrated all clinical manifestations of phenylhydroxylamine-induced erythrocyte oxidant stress. Severe methemoglobinemia was present, though unrecognized, within 90 min of ingestion of the shoe dye. The elevated serum K^+ may have reflected extracellular shift from acidosis or release of this ion into serum from hemolyzed red blood cells. The presence of RBC fragments supports early hemolysis. The mildly elevated AST and ALT, and possibly the prolonged prothrombin time, may have represented pre-existent liver disease or resulted from mild liver injury due to poor oxygen delivery to hepatocytes. Repeat transaminase levels several hours after administration of methylene blue revealed normalization of these values. Hyperglycemia may have been caused from the stress hormone

response, but may also have been due to previously undiagnosed diabetes mellitus. Blood sugars remained mildly elevated throughout the remainder of the hospitalization.

We believe that the major cause of the patient's rapid clinical deterioration was the exceedingly high methemoglobin level, in conjunction with formate toxicity. The refractory nature of the methemoglobinemia and the development of hemolytic anemia were not unexpected, as both have been described after aniline ingestion (7).

CONCLUSION

Although methanol and aniline poisoning each have been reported, we describe a unique case of combined toxicity after ingestion of shoe dye. Clinicians should be aware of the possibility of both toxicities in patients who ingest similar products.

REFERENCES

1. Barceloux DG, Bond R, Krenzelok EP, Cooper H, Vate JA. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol 2002;40: 415–46.
2. Harrison RJ. Occupation and environmental gases. Chemicals and gases. Prim Care 2000;27:917–82.
3. Seiger DL, Hantsch CE. Methemoglobin-forming compounds. In: Sullivan JB, Krieger GR, eds. Clinical environmental health and toxic exposures, 2nd edn. New York: Lippincott Williams and Wilkins; 2001:727–33.
4. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology and clinical management. Ann Emerg Med 1999;34:646–56.
5. Langford JS, Sheikh S. An adolescent case of sulfhemoglobinemia associated with high-dose metoclopramide and N-Acetylcysteine. Ann Emerg Med 1999;34:538–41.
6. Tabbara IA. Hemolytic anemias. Diagnosis and management. Med Clin North Am 1992;76:649–68.
7. Iwersen-Bergmann S, Schmoldt A. Acute intoxication with aniline: detection of acetaminophen as aniline metabolite. Int J Legal Med 2000;113:171–4.