Empiric Treatment of Cyanide Toxicity in an Enclosed-Space Fire Survivor

Authors: David Dinh, PharmD, BCPS, and Jamie M. Rosini, PharmD, BCPS, Newark, DE
Section Editor: Allison A. Muller, PharmD, D.ABAT

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Background

Cyanide is a chemical compound that contains a cyano group—a carbon molecule that shares a triple bond with a nitrogen molecule. It can exist as a salt, liquid, or gas, and it is sometimes identified as having a bitter almond smell but may also be odorless. Cyanide is one of the most rapidly acting and deadly poisons, and signs and symptoms of cyanide toxicity can manifest within seconds to minutes depending on the route and duration of exposure. Sources of cyanide include insecticides, jewelry cleaners, fruit seed pits, cigarette smoke, automobile exhaust, smoke inhalation in enclosed-space fires, and medications such as sodium nitroprusside.[1]

Case Study

A 50-year-old woman with suspected cyanide poisoning presented to the emergency department by emergency medical services (EMS). She reported waking up in a smoke-filled house and was able to quickly exit the home, but she reentered the burning home to search for her partner, who was still inside. When EMS arrived to the scene, the patient was completely covered in soot and smoke but denied any difficulty breathing. She underwent placement of on a non-rebreather mask delivering 100% oxygen at a rate of 15 L/min. While en route to the emergency department, she was nauseated and was treated with ondansetron. Vital signs obtained by EMS included a heart rate of 120 beats/min, blood pressure of 160/80 mm Hg, respiratory rate of 22 breaths/min, and oxygen saturation of 97%. A carbon monoxide monitor was attached to the patient with an average reading of 11% (range, 7%-13%; normal range, <2.5% for a nonsmoker or <10.0% for a smoker). On the patient's arrival to the emergency department, her vital signs remained stable, but she had difficulty breathing and a frequent productive cough with pink sputum developed. Laboratory tests included a basic metabolic panel with findings within normal limits; lactate level, 0.7 mmol/L (normal range, 0.5-2.2 mmol/L); and carboxyhemoglobin level, 12% (normal range, <3%). The carbon monoxide and carboxyhemoglobin levels were considered normal for this patient because she was a smoker. Assessment of her cyanide level was requested from an outside laboratory, and 5 g of hydroxocobalamin was empirically administered because the patient had difficulty breathing and was completely covered in soot.

Pathophysiology of Cyanide Toxicity

In cyanide toxicity, it is particularly important to recognize that the oxygen supply is adequate but extraction of oxygen to cells is impaired. Cyanide binds to and inactivates several enzymes, including mitochondrial cytochrome oxidase a_3 (cellular hypoxia), carbonic anhydrase (inhibition of acid-base balance), and glutamate decarboxylase (induction of seizures), and it binds to iron with a stronger affinity than oxygen.[2–4] The primary cause of cyanide toxicity lies within the impaired function of mitochondrial cytochrome oxidase a_3. Cyanide binds to the ferric ion portion of cytochrome oxidase a_3, the last enzyme in the mitochondrial electron transport chain, preventing aerobic metabolism and formation of adenosine triphosphate (ATP).[2] Under normal circumstances, hydrogen ions bind with oxygen to produce ATP, but because of the disruption of the utilization of oxygen, there is an excess of hydrogen ions and the formation of ATP via aerobic metabolism is decreased.[5] This results in a shift to anaerobic metabolism, leading to increased production of lactic acid. The increased concentration of lactate in combination with excess hydrogen ions ultimately leads to acidosis and cell death.

David Dinh is Postgraduate Year 2 Critical Care Pharmacy Resident, Christiana Care Health System, Newark, DE.

Jamie M. Rosini is Clinical Pharmacist, Emergency Medicine, Christiana Care Health System, Newark, DE.

For correspondence, write: David Dinh, PharmD, BCPS, 4755 Ogletown-Stanton Rd, Pharmacy Administration LE15, Newark, DE 19718; E-mail: ddinh@christianacare.org.

J Emerg Nurs 2014;40:282-5.

Available online 31 March 2014.

0099-1767/$36.00

http://dx.doi.org/10.1016/j.jen.2014.02.003

Early signs and symptoms of cyanide toxicity include anxiety, headache, confusion, bright red retinal veins, tachypnea, and tachycardia. Ongoing hypoxia results in late manifestations, such as altered levels of consciousness, seizures, paralysis, coma, hypoventilation, apnea, hypotension, electrocardiogram changes, and death.[6]

Treatment of Cyanide Toxicity

The treatment of cyanide toxicity is 3-fold: decontamination, supportive care, and antidotal therapy.[7] Decontamination includes the removal of the source of cyanide exposure (eg, enclosed fire), removal of contaminated clothing, and rinsing the skin in the event of dermal exposure. Supportive care consists of basic or advanced life support, if required, and administration of 100% oxygen. Available antidotal therapies include sodium nitrite in combination with sodium thiosulfate or hydroxocobalamin.

The first kit approved by the Food and Drug Administration for the treatment of cyanide toxicity was the cyanide antidote kit, a 3-drug antidote containing amyl nitrite, sodium nitrite, and sodium thiosulfate. Sodium nitrite and sodium thiosulfate are intravenous infusions, whereas amyl nitrite is an inhalant and is beneficial when there is a delay in obtaining intravenous access. This antidote kit has since been removed from the market, but a new kit containing a 2-drug regimen, sodium nitrite and sodium thiosulfate (Nithiodote; Cangene BioPharma, Inc., Baltimore, Maryland), is now available. Nithiodote contains 300 mg/10 mL (30 mg/mL) of sodium nitrite, infused over a period of 2 to 4 minutes, and 12.5 g/50 mL (250 mg/mL) of a sodium thiosulfate solution, which should be infused over a period of 10 to 20 minutes immediately after the administration of sodium nitrite.[8] Amyl nitrite and sodium nitrite create methemoglobin by converting the iron in hemoglobin from the ferrous to the ferric form.[2] Although methemoglobin does not have oxygen-carrying capacity, it has a higher affinity for cyanide than cytochrome a_3 in the mitochondria, resulting in the formation of cyanomethemoglobin.[9] This leads to a reduction in the serum cyanide level, allowing the reactivation of the mitochondrial electron transport system and thus reestablishing aerobic metabolism. Adverse effects of nitrite administration include hypotension and the risk of impairing oxygen delivery to tissues via the formation of methemoglobin.

Amyl nitrite and sodium nitrite are used in combination with sodium thiosulfate to enhance the clearance of cyanide from the body. Sodium thiosulfate donates sulfur to cyanide via the rhodanese-catalyzed formation of thiocyanate, a less toxic compound that is excreted in the urine.[2] Though fairly well tolerated, sodium thiosulfate is associated with hypersensitivity reactions and rate-dependent hypotension. Disadvantages of sodium thiosulfate include its poor penetration of the mitochondrial membrane and a delayed onset of action. It also has the potential to accumulate in patients with renal failure, causing degradation of thiocyanate, resulting in thiocyanate reverting to unbound cyanide.[9–11]

In 2006 the Food and Drug Administration approved the second treatment for cyanide poisoning, hydroxocobalamin (Cyanokit; Merck Santé s.a.s., Semoy, France). Hydroxocobalamin is an endogenous vitamin B_{12} precursor that binds to unbound cyanide to form cyanocobalamin (vitamin B_{12}) and is excreted by the kidneys.[12] It is administered as a 5-g infusion over a period of 15 minutes; a second 5-g dose may be administered, if required, for a maximum total of 10 g.[13] A prospective, observational case series by Borron et al[14] examined the effects of hydroxocobalamin in 69 patients with acute cyanide poisoning due to smoke inhalation. Patients were included if they were aged at least 15 years; had soot present in the mouth, nose, or expectorations; had altered neurologic status; and were admitted to the intensive care unit. Of patients admitted to the intensive care unit, 72% (50 of 69 patients) survived after hydroxocobalamin administration. Forty-two patients had confirmed cyanide poisoning (>39 μmol/L), with 28 patients (67%) surviving after administration of hydroxocobalamin. Hydroxocobalamin has been proved to be safe when administered in the prehospital setting, even if the diagnosis of cyanide toxicity is incorrect.[15] Hydroxocobalamin has the added advantage of not compromising the oxygen-carrying capacity of hemoglobin, and it has been shown to readily cross the blood-brain barrier in animal studies, potentially providing greater benefit and limiting the potential for neurologic damage.[9] Adverse effects of hydroxocobalamin include transient hypertension and reddish discoloration of the skin and urine, which may last for several days.[9,10] Other complications associated with hydroxocobalamin include interference with chemistry assays (spectral effects), measurements with co-oximetry, and hemodialysis ("blood-leak" errors).[16,17]

Case Outcome

The patient presented with minor signs of cyanide toxicity, including nausea, anxiety, tachypnea, and tachycardia. She was treated empirically for cyanide poisoning with hydroxocobalamin and subsequently admitted to the emergency department's 24-hour observation unit. Her blood pressure was 142/72 mm Hg before receiving hydroxocobalamin, and