Cyanide Poisoning

Introduction

Swedish chemist Carl Wilhelm Scheele first isolated cyanide in 1782. He reportedly died due to cyanide poisoning in 1786. Since that time cyanide has earned its reputation as a powerful and deadly poison. Fear of cyanide is augmented by its quick and lethal action, and numerous sources. Cyanide was used on the battlefield by Napoleon III, during the First World War, and by the Germans in World War II. Cyanide was publicized again in 1978 with the mass suicide in Jonestown when more than 900 people died, and in 1982 with seven reported deaths due to cyanide-tainted acetaminophen. Concern for cyanide’s potential as a weapon of terror continues to loom, and it is recognized as a possible chemical weapon by the Centers for Disease Control. Currently, however, cyanide exposures are most likely to occur due to products of combustion of many household materials (including nylon, wool, silk and many plastics), or due to laboratory or industrial use. Cyanide is often described as having an odor of “bitter” almonds; however, this odor is detectable by only 60% of the general population.

Case presentation

A 53-year-old male presents to the emergency department after a suicide attempt. He called his fiancé telling her of his intentions to drink sodium cyanide, which he had mixed in a light beer. His fiancé immediately notified EMS, who arrived within 5 minutes to find the patient awake and alert, but anxious and tachypneic. During the several minute transport to the emergency department (ED) the patient became confused, then obtunded. He then quickly stopped breathing in the ambulance, and upon arrival to the ED had no pulse. Once connected to the monitor he was found to be in a sinus bradycardia. CPR was initiated, the patient was intubated and administered epinephrine and atropine. He regained a pulse. The patient was administered sodium nitrite and sodium thiosulfate from a cyanide antidote kit in the ED. Within minutes the patient was awake and following simple commands. His initial ABG reflected a metabolic acidosis with a pH of 6.79 and bicarbonate of 8 mEq/L. After 1 hour and 2 ampules of sodium bicarbonate the patient’s pH was 7.34 with a bicarbonate of 28 mEq/L. Overnight the patient’s laboratory studies remained within normal limits and he was extubated the
following morning. After a brief period of observation he was transferred to a psychiatric facility.

Questions:
1. Is this a typical time course for cyanide poisoning?
2. How did the patient obtain cyanide, and what are common sources of exposure?
3. What antidotes are available for cyanide?

Epidemiology
Cyanide is widely used as a reagent in laboratory and industrial settings. Cyanide salts are commercially available for use as jewelry cleaner (though the industry is moving away from its use for obvious reasons). In 2006 The American Associations of Poison Control Centers reported 215 exposures and 7 deaths from cyanide. The majority of cyanide exposures are unintentional, involving chemists or laboratory workers (where cyanide is used as a common reagent), or through the production of cyanide due to combustion of common household materials during fires. Cyanide can be found as a gas (hydrogen cyanide), or salt (potassium cyanide, sodium cyanide). Certain chemicals such as acetonitrile (found in artificial fingernail remover), and acrylonitrile are metabolized by the liver into cyanide. Many plants contain cyanogenic glycosides that are metabolized into cyanide. The pits and seeds of “stone” fruit (such as apricots), almonds, and cassava contain amygdalin, a cyanogenic glycoside. Amygdalin has been used medicinally in the form of the controversial antineoplastic agent Laetrile. Nitroprusside infusions may also be a source of iatrogenic cyanide poisoning. Each nitroprusside molecule contains five molecules of cyanide, which slowly dissociate from the parent compound. Although these cyanide metabolites are neutralized endogenously, some malnourished or postoperative patients may have depleted concentrations of precursors necessary for neutralization, leading to accumulation of cyanide and clinical toxicity.

Pathophysiology
Cyanide is an inhibitor of multiple enzymes, including succinic acid dehydrogenase, superoxide dismutase, carbonic anhydrase, and cytochrome oxidase. Cytochrome oxidase is a critical enzyme of aerobic respiration, generating ATP from the cellular metabolism of glucose. In the electron transport chain, cytochrome oxidase aa3 (also known as cytochrome c oxidase) is responsible for delivering electrons and free hydrogen ions to oxygen molecules in the final steps of aerobic respiration. Cyanide directly inhibits cytochrome oxidase aa3, and blocks the routine transfer of electrons and free hydrogen ions to oxygen, thus paralyzing both oxidative phosphorylation and cellular metabolism. Subsequently, the accumulation of free hydrogen ions initiates acidemia, as cellular metabolism shifts from aerobic respiration to anaerobic respiration, leading to increased production of lactic acid. The final result is severe metabolic acidosis, severely impaired glucose and oxygen consumption, and hypoxic cell death. Because oxygen is unused by tissues, blood gas measurements of venous blood will
often reveal higher-than-normal partial pressures of oxygen.

Trace cyanide production occurs daily in the liver, and is routinely detoxified by an endogenous enzyme, rhodanese, that binds free cyanide with a sulfur moiety to form thiocyanate. Thiocyanate is then excreted by the kidneys. In cyanide poisoning, body reserves of sulfur are rapidly depleted. In addition, cyanide-induced increases in cytosolic calcium, diminished ATP production, and the production of reactive oxygen species lead to inactivation of rhodanese.

Poisoning may occur by inhalation of hydrogen cyanide gas, or by ingestion of inorganic cyanide salts or cyanogenic chemicals. Cyanide salts in solution may be absorbed through the skin.

**Clinical presentation**

Clinically, an abrupt onset of profound toxic effects shortly after exposure is characteristic. Symptoms may include headache, nausea, dyspnea, and confusion, followed quickly by syncope, coma, abnormal respirations, seizures, and cardiovascular collapse. Skin may be pale or blue secondary to impaired circulation; in some cases, the skin may have a pink hue, secondary to accumulation of unused oxygen in the venous circulation. When cyanide is ingested in the form of a salt, a brief delay in symptom onset may be seen. Longer delays may occur with cyanogenic chemicals such as acetonitrile that require metabolism to become active within the body. Toxicity from these cyanogenic compounds may not be evident for hours.

Patients on nitroprusside infusions may develop cyanide toxicity over hours to days, especially in patients on infusions greater than 2 μg/kg/min and with poor dietary stores of sulfur donors necessary for detoxification. Thiocyanate is the byproduct of detoxification of cyanide by rhodanese and is usually renally secreted but may build up in patients on nitroprusside with poor renal function. The symptoms of thiocyanate toxicity are nonspecific and may include alterations in mental status, nausea, vomiting, fatigue and seizures. In severe thiocyanate toxicity hemodynamic instability and increased intracranial pressure may occur. Thiocyanate can be removed by hemodialysis.

**Diagnosis**

Diagnosis of cyanide poisoning is based on a history of exposure, or the presence of rapidly progressing symptoms. Differential diagnoses include poisoning by hydrogen sulfide and sodium azide. Hydrogen sulfide is found as a component of sewer gas and is notable for its rotten egg odor. Sodium azide is used as a propellant for the deployment of air bags and as a preservative in laboratories. Classically, an odor of bitter almonds has been associated with cyanide poisoning, however only 40-60% of the population is able to detect this odor. Severe lactic acidosis usually occurs quickly in victims with a significant cyanide exposure. Measured venous oxygen tension may be elevated due to blocked utilization. “Cherry red” mucosa has been classically described in cyanide poisoned patients, but this occurrence is variable. A more reliable finding is the loss of color differentiation between retinal arteries and veins on fundoscopic examination. This is due to the inability for cyanide-affected retinal cells to utilize
oxygen, thus increasing oxygen saturation in the retinal veins. Specific blood cyanide levels are obtainable (usually sent out by the hospital laboratory), but are rarely clinically helpful in the early and most crucial management of these cases.

In patients on infusions of nitroprusside, cyanide levels may be measured to monitor toxicity; however, patients may have elevated cyanide levels without signs of toxicity due to sequestration of cyanide in red blood cells. In such cases secondary markers such as blood pH or bicarbonate should be used in monitoring for toxicity. Thiocyanate levels are available and may be useful in monitoring patients at risk for developing thiocyanate toxicity, such as those with compromised renal function.

**Treatment**

Initial treatment of cyanide poisoning includes airway management, oxygenation, intravenous fluid administration, and cardiopulmonary resuscitation. Two antidote kits are available to treat cyanide poisoning. The most well known cyanide antidote kit (manufactured by Lily, Taylor, and others), consists of amyl nitrite, sodium nitrite and sodium thiosulfate. Amyl nitrite (which is given by inhalation) and sodium nitrite (300 mg or 10 mg/kg given intravenously) are administered to induce modest methemoglobinemia. Cyanide binds more avidly to the methemoglobin molecule than to the cytochrome complex of mitochondrial membranes. When cyanide binds to methemoglobin, a relatively less toxic cyano-methemoglobin is formed. Sodium thiosulfate (50 mL of a 25 percent solution [12.5 g] or 1.65 mL/kg intravenously) acts as a sulfur donor for rhodanase, allowing more efficient and rapid conversion of free cyanide to the less toxic thiocyanate.

A more recently available commercial cyanide antidote kit consists of hydroxocobalamin (Cyanokit, Dey pharmaceuticals), a precursor of vitamin B12, which contains a cobalt moiety that avidly binds to intracellular cyanide, forming cyanocobalamin (vitamin B12). This molecule is stable, with minimal toxicity and is readily excreted in the urine. A dose of 50 mg/kg, or 5 g, intravenously is effective for the majority of adult patients. Although optimum pediatric dosing of the Cyanokit has not been established, some sources recommend 70 mg/kg intravenously. Hydroxocobalamin may be more beneficial than traditional nitrite-containing kits in patients who may react poorly to the formation of methemoglobin, such as those with coexisting high levels of carboxyhemoglobin or patients with G-6-PD deficiency.

**Discussion of case questions**

1. Is this a typical time course for cyanide poisoning?

Given that the patient ingested a solution of a cyanide salt (e.g. NaCN, KCN), a delay of onset and progression of signs and symptoms over a course of minutes can be seen. This is different from cyanide gas exposure (i.e. HCN), in which the onset and progression of symptoms may occur within seconds.
2. How did the patient obtain cyanide, and what are common sources of exposure?

The patient obtained sodium cyanide marketed as jewelry cleaner many years ago when he worked as a jeweler. Cyanide is also used extensively in photography developing. Most inhalational exposures to cyanide are due to house fires, or exposure in laboratory or industrial settings.

3. What antidotes are available?

In the United States there are two kits commercially available for treatment of cyanide poisoning. The traditional kit consists of amyl nitrite, sodium nitrite, and sodium thiosulfate. The newer kit contains hydroxocobalamin. Head-to-head comparisons of these kits have not been performed; however, both products are efficacious in human case reports and animal models.

Consultation assistance

Consultation with a specialist in poison information or with a medical toxicologist can be obtained free of charge by calling the California Poison Control System at 1-800-222-1222.

This issue of CALL US... was written by Alexander D. Miller, MD

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The California Poison Control System is operated by the School of Pharmacy, University of California, San Francisco. (callus@calpoison.org)