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Background

Cyanide is a naturally occurring chemical, found in many plants, that has been used in conventional warfare and poisoning for more than two millennia.[1] It is highly lethal, whether inhaled as a gas, ingested in solid form, or absorbed through topical exposure. Two notable incidents in recent history include the Jonestown Massacre in 1978 and the Tylenol poisonings in 1982, which highlight the lethality of this poison. Despite its historical use as a chemical warfare agent, the most common cause of cyanide poisoning is smoke inhalation from fires.

First isolated in 1782, cyanide is a compound composed of carbon atom triple-bonded to a nitrogen atom (C≡N). Cyanide is a naturally occurring chemical can be produced by certain types of bacteria, fungi, and algae and found in several types of plants, seeds, and fruit stones, including bamboo, cassava, bitter almonds, apples, and peaches. Despite its toxicity, cyanide has many roles in industry and medicine. In industry, it is used in manufacturing, pesticides, and can be found in several industrial chemicals.[2,3] In medicine, cyanide can be found in the widely used antihypertensive sodium nitroprusside, each molecule of which contains 5 ions of cyanide.

Use as Chemical Warfare Agent

Because it is a fast-acting and highly lethal chemical, cyanide poses an ongoing threat as a weapon of terrorism, whether it is delivered in oral form via sodium cyanide and potassium cyanide or as a gas via hydrogen cyanide and cyanogen chloride.

The use of cyanide in warfare dates to Roman Emperor Nero (37–68 CE), who used cyanide-containing cherry laurel water as a poison. Cyanide was also used during the Franco-Prussian War (1870–1871), during which Napoleon III urged his troops to dip their bayonet tips in the poison. Both World Wars saw the use of cyanide: during World War I, it was employed by French and Austrian troops; during World War II, Nazi Germany used the rodenticidal product Zyklon B to kill millions of people. In the 1980s, cyanide may have been used in the Iran-Iraq War, on the Kurds in Iraq, and in Syria. In 1995, the Japanese cult Aum Shinrikyo placed cyanide in subway bathrooms.

Mechanism of Action and Toxicokinetics

Cyanide poisons the mitochondrial electron transport chain within cells and renders the body unable to derive energy (adenosine triphosphate—ATP) from oxygen.[4] Specifically, it binds to the a3 portion (complex IV) of cytochrome oxidase and prevents cells from using oxygen, causing rapid death.

Airborne release of cyanide gas, in the form of hydrogen cyanide or cyanogen chloride, would be expected to be lethal to 50% of those exposed (LC*t*50) at levels of 2,500–5,000 mg•min/m^3 and 11,000 mg•min/m^3, respectively. When ingested as sodium or potassium cyanide, the lethal dose is 100–200 mg.

Signs and Symptoms

Cyanide kills quickly; death occurs within seconds of a lethal dose of cyanide gas and within minutes of ingestion of a lethal dose of cyanide salt.[2] The central nervous system (CNS) and cardiovascular systems are chiefly affected. Signs and symptoms of cyanide poisoning include the following:

- **CNS**: headache, anxiety, agitation, confusion, lethargy, seizures, and coma
- **Cardiovascular**: decreased inotropy, bradycardia followed by reflex tachycardia, hypotension, and pulmonary edema
- **Other**: acute lung injury, nausea and vomiting, cherry-red skin color.

Survivors may suffer Parkinson's disease, ataxia, optic atrophy, and other neurologic disorders.

Diagnosis

Cyanide intoxication is largely a clinical diagnosis; however, several laboratory features are suggestive:

- Metabolic acidosis (increased anion gap)
- Elevated lactic acid
- Venous oxygen saturation > 90%.

Cyanide blood levels are confirmatory, as results are not obtainable in time for initial diagnosis.[1] There are some reports of use of rapid calorimetric paper test strips to confirm the presence of cyanide.

Countermeasures

Before cyanide antidote can be administered, the patient must be removed from the cyanide-laden area, clothing removed, and skin washed with soap and water. If cyanide salts have been ingested, activated charcoal may prevent absorption from the gastrointestinal tract.

Management of cyanide toxicity is based on the principle of reversing and/or displacing cyanide binding to cytochrome a3. There are two major modalities of treatment: hydroxocobalamin and the cyanide antidote kit containing sodium nitrate and sodium thiosulfate.[5]

- **Hydroxocobalamin (Cyanokit)**: The preferred antidote, based on a 2018 US Food and Drug Administration (FDA) expert consensus panel, is the Cyanokit, containing lyophilized hydroxocobalamin and other products used for intravenous infusion. Hydroxocobalamin contains cobalt, to which cyanide has a strong binding affinity. The reaction of hydroxocobalamin with cyanide produces cyanocobalamin (vitamin B12) that is then excreted in the urine.
- **Cyanide Antidote Kit**: The primary components of these kits include sodium nitrate and sodium thiosulfate.[6] When administered intravenously, sodium nitrate and sodium thiosulfate release cyanide from cytochrome a3 by providing a target for which cyanide has a higher attraction. IV sodium nitrate reacts with hemoglobin to cause the formation of

methemoglobin, for which cyanide has a high binding affinity. Sodium thiosulfate provides a source of sulfur that the enzyme rhodanese—the major pathway for metabolism of cyanide—utilizes to detoxify cyanide.

Recovery

Although recovery from a chemical attack is rare, victims may survive sub-lethal exposures, whether from ingestion, smoke inhalation, or exposure to cyanide-containing industrial products. Patients who are treated successfully for cyanide poisoning should be observed for development of long-term neuropsychiatric symptoms that are similar to symptoms experienced by survivors of cardiac arrest or carbon monoxide poisoning.

References

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