CYANIDE TOXICITY AND TREATMENT

by Charles Hall, PharmD

Introduction

Hydrogen cyanide gas is a common by-product of incomplete combustion of plastics such as polyurethanes and nitrocellulose, synthetic material such as nylon, and natural materials such as wool and silk. Exposure from residential fires is a common cause of cyanide poisoning in western countries. Inorganic salts and salt solutions of cyanide are used in metal plating and extraction of precious metals. Cyanogens are naturally occurring or synthesized compounds. The synthesized forms are aliphatic nitriles used in a number of solvents. Amygdalin is a naturally occurring cyanogen that is found in apricot pits, apple seeds and cherry pits.

There are two antidotes for the treatment of cyanide toxicity. The traditional antidote is a multi-component kit (Cyanide Antidote Package®) that consists of amyl nitrite, sodium nitrite and sodium thiosulfate. The single agent antidote recently approved by the FDA is hydroxocobalamin (Cyanokit®).

Pharmacokinetics of cyanide

Absorption of cyanide can take place via inhalation, ingestion and through the skin. Inhalation results in the most rapid absorption (seconds), followed by ingestion (minutes to hour), then transdermal. Cyanide is rapidly distributed to all organs. The initial burden binds to endogenous methemoglobin and then, to a lesser extent, normal hemoglobin.

Cyanide is detoxified by the rhodanese enzyme, which catalyzes the reaction of endogenous thiosulfate with cyanide to form thiocyanate. To a much lesser extent endogenous hydroxocobalamin binds to cyanide and forms cyanocobalamin (vitamin B₁₂). Thiocyanate and cyanocobalamin are renally excreted. Cyanocobalamin can also be excreted in the bile.

Pharmacology/toxicology of cyanide

Cyanide is a chemical asphyxiant. Cyanide toxicity occurs when cytochrome oxidase-₃ is bound by cyanide, inactivated and oxidative phosphorylation is blocked. Aerobic utilization of oxygen is impaired and cellular asphyxia ensues.

Pre-hospital, Supportive measures, Monitoring/ Diagnosis

All cyanide exposures should be considered potentially lethal. Clinical manifestations related to hypoxia and may include nausea, vomiting, weakness, shortness of breath, drowsiness, chest discomfort, seizures, coma and death. Flushing can be a manifestation of cyanide toxicity and is due to the larger amount of oxygen in the venous system as a result of the impaired oxygen utilization. Metabolic acidosis, high lactate, hypotension with bradycardia or tachycardia, and dysrhythmias are indicators of a more severe poisoning. Treatment starts with maintaining an open-airway and ventilatory support if necessary. Antidotal treatment should not be delayed for lab results. Monitor the patient’s acid-base status, serum lactate, and electrolytes. Blood cyanide concentrations are not readily available for diagnostic or treatment purposes.

Antidotes Cyanide Antidote Package®

The mechanism of action is to induce mild methemoglobinemia with nitrates to halt the transfer of cyanide to the tissues. Cyanide has a greater affinity for the ferric ion (Fe³+) in methemoglobin than the ferrous ion (Fe²+) in cytochrome oxidase.

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In 2007, the Utah State Legislature passed a bill that established a 2-year program to reduce unintentional deaths from prescription opiates.

The goals are:

- Reduce the number of deaths due to prescription pain medications by 15% by 2009 by educating providers, patients, insurers, and the public.
- Improve understanding of occurrence of deaths related to prescription pain medications and understand prescribing patterns and other risk factors that increase risk of death.
- Provide recommendations regarding use of the Controlled Substance Database Program to identify risks and potentially to prevent deaths due to prescription pain medications.

Several milestones have been accomplished to the above goals:

- Provider education is being done in small group trainings, large group presentations, and mass mailings.
- A statewide media campaign was launched in May 2008 with the slogan “Use Only As Directed.” TV and radio spots have aired. Bookmarks, posters, informational pamphlets, clings (re-usable stickers), and newspaper ads have been developed and distributed statewide. Visit www.useonlyas-directed.org for more information.
- A new research project, to take place at the Office of the Medical Examiner, was designed to examine risk factors associated with overdose deaths involving prescriptons. Other research using death certificate information and emergency department encounters related to overdoses will be analyzed.

Even though the number of non-illicit overdose deaths has been more stable in the past 3 years, emergency department encounters involving opioids has continued to increase. Deaths have occurred in 11 of the 12 local health districts in the state. Martin Caravati serves on the Pain Management Steering Committee and Marty Malheiro serves on the Patient & Community Education Work Group.

Check out our website for more poison prevention information at www.utahpoisoncontrol.org

**NATIONAL POISON PREVENTION WEEK**

**MARCH 15-21, 2009**

The purpose of National Poison Prevention Week is to increase awareness to the dangers of poisonings and how to prevent poisoning. The theme of NPPW is; “Children Act Fast…So Do Poisons”.

Please join us in celebrating this important week by promoting awareness to potential poisonings and poison prevention by distributing poison prevention materials to your patients.

Contact the Utah Poison Control Center to obtain posters and other educational materials.

**Call FAST to treat a poisoning!**

**Call FIRST to prevent a poisoning!**

1-800-222-1222

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**Cyanide Toxicity and Treatment**

Sodium thiosulfate is subsequently administered and donates its sulfur group to form thiocyanate. Thiocyanate is much less toxic and is excreted in the urine.

The components of the cyanide antidote kit are: **Amyl nitrite**- if the patient is breathing spontaneously, break an ampule in a handkerchief and hold it in front of the victim’s mouth for 15-30 seconds, then let patient rest for 30 seconds. Re-administer until IV sodium nitrite can be administered. **Sodium nitrite**-

- discontinue amyl nitrite and administer 300 mg IV (10 ml of 3% solution) over 5 minutes. Pediatric dose is 6-10 mg/kg (0.2-0.33 ml/kg 3% solution). Sodium nitrite infusion should be stopped upon clinical improvement or severe methemoglobinemia. Monitor for hypotension or signs of excessive methemoglobin. **Sodium thiosulfate** - immediately after sodium nitrite, administer sodium thiosulfate 12.5 gm IV for an adult. Pediatric dose is up to 400 mg/kg not to exceed 12.5 gm. Sodium thiosulfate may be used alone to treat sodium nitroprusside induced cyanide poisoning or concurrently for prevention.

**Hydroxocobalamin Antidote**

In Europe hydroxocobalamin (Cyanokit®) has been used for many years for cyanide toxicity and has recently become available in the U.S. Hydroxocobalamin detoxifies cyanide by forming cyanocobalamin or vitamin B12, which is excreted in the urine. Hydroxocobalamin binds in an equimolar manner to cyanide.

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Cyanide Toxicity and Treatment

The initial dose is 5g IV. Additional doses of 2.5 g may be given as needed for a total of 10g. The elimination half-life of hydroxocobalamin is approximately 26-31 hours. Adverse effects following hydroxocobalamin were evaluated in healthy volunteers and were felt to be tolerable given the life-threatening nature of cyanide poisoning. Adverse effects included an increase in systolic blood pressure of 22-27 mmHg and skin redness which usually occurred within several minutes after infusion. The increase in blood pressure may actually be beneficial in a patient who is hemodynamically unstable. Other less common adverse effects noted were pustular rash, headache, erythema at the injection site, a decrease in lymphocyte percentage, nausea, pruritus, chest discomfort and dysphagia.

Conclusion

Hydroxocobalamin is a new antidote available in the United States for the treatment of cyanide poisoning. It offers an advantage over the traditional multi-component antidote kit through its ease of administration and limited side effect profile.

Bibliography


DID YOU KNOW?

In 2007, the Consumer Products Safety Commission (CPSC) evaluated home lead testing kits. The CPSC does not recommend the use of these kits because testing has shown that some kits may not reliably detect lead when it is present (false negatives) or may register a positive response in the absence of significant lead levels (false positive).

The FDA issued a Public Health Advisory for parents and caregivers, recommending that over-the-counter (OTC) cough and cold products should not be used to treat infants and children less than 2 years of age because of serious life threatening side effects (FDA News, 1/17/08). Recently in an FDA Statement issued October 8, 2008 this information was updated. The Consumer Healthcare Products Association (CHPA) has announced that it’s members are voluntarily modifying the product labels for consumers of OTC cough and cold medicines to state “do not use” in children under 4 years of age.

The UPCC was one of the first three Poison Centers established in the United States. Establish in 1954, the UPCC has responded to over one million calls for assistance.

POISON PEARLS

INTRAVENTRICULAR CONDUCTION DELAY AND SODIUM CHANNEL BLOCKER TOXICITY

Natalie Silverton, MD  
Emergency Medicine Resident

Intraventricular conduction delay (IVCD) is the diffuse slowing of cardiac conduction causing a uniform delay in the activation of the ventricular myocardium represented on the EKG as a widened QRS (>100 ms). IVCD is classically seen with tricyclic antidepressant (TCA) drug overdose, but is also a feature of sodium channel blocker toxicity in general. In the normal cardiac myocyte, the action potential is spread by sequential activation of voltage gated sodium channels. Sodium channel blockers reduce the influx of sodium, thereby slowing depolarization and causing a widened QRS. Drugs that cause sodium channel blockade are numerous and diverse. The most obvious examples are the class I antiarrhythmics such as quinine, procainamide, flecainide, and propafenone. Other examples include amantadine, antihistamines, propranolol, cocaine, phenothiazines, and TCAs. Overdose from any of these drugs can produce IVCD, which can be manifested as a bradyarrhythmia or wide complex tachycardia depending on the other underlying properties of the drug. TCAs, diphenhydramine, and phenothiazines will often produce tachycardia in overdose because of their anticholinergic properties. The management of sodium channel blocker toxicity includes intravenous sodium bicarbonate administration, which has been shown to narrow the QRS interval, control ventricular arrhythmia, or reverse hypotension. Hypotension should also be treated with judicious fluid resuscitation (myocardial depression caused by sodium channel blockade makes fluid overload more likely), and norepinephrine or epinephrine if hypotension persists despite sodium bicarbonate and IV fluid therapy. Ventricular arrhythmias can be treated with lidocaine or amiodarone if sodium bicarbonate is ineffective. Case reports have supported using hypertonic saline when sodium bicarbonate has been ineffective and the serum pH is > 7.55. Other causes of IVCD include hyperkalemia, myocardial ischemia, or left ventricular hypertrophy and should also be considered in the patient presenting with a wide QRS.

The FDA has announced that it’s members are voluntarily modifying the product labels for consumers of OTC cough and cold medicines to state “do not use” in children under 4 years of age.
**Toxins in the News**

**Fomepizole**, the antidote for ethylene glycol and methanol poisoning, is now available generically. Hospitals can now obtain single vials of fomepizole in addition to traditional package that includes 4 vials.

Illicitly manufactured **fentanyl** has resulted in an epidemic of deaths in multiple states, including NJ, MD, IL, MI and PA. It is sold on street drug markets for its heroin-like effect and is often mixed with heroin or cocaine.

The FDA added a BOXED WARNING about the increased risk of developing tendinitis and tendon rupture in patients taking **fluoroquinolones**. This risk is further increased in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy.

The American Heart Association advises obtaining an EKG before beginning treatment using **stimulant drugs in children** with attention deficit hyperactivity disorder (ADHD) whenever possible in order to detect unknown heart conditions that could lead to cardiac events.

**Energy drinks** are sold as dietary supplements, and the FDA doesn’t limit **caffeine** content or require warnings. A typical 12-ounce soft drink contains about 35 mg of caffeine, a 6-oz cup of brewed coffee ranges from 77 to 150 mg, while some energy drinks have as much as 500 mg of caffeine.

**Meet the UPCC Staff**

**MO MULLIGAN RN, BSN, JD** has been a Specialist in Poison Information at UPCC since July 2007. Mo is occasionally known by her real name of Maureen. Mo has been an ICU nurse since 1974. She first worked with a poison control while at Hennepin County Medical Center as a staff nurse in the Medical Intensive Care Unit. Since then, Mo received her bachelor’s degree in nursing from the University of Minnesota and her law degree from William Mitchell College of Law. Mo has worked as an attorney doing medical malpractice defense work and then as a manger of a coronary care unit. She came to Utah to be the Director of St. Mark’s Hospitals ICUs in 1992. In 1998, she started working at the University of Utah Hospitals and Clinic’s as the Director of Performance Improvement overseeing support for quality and patient safety. Since joining UPCC Mo says the biggest challenge is the learning curve, the UPCC specializes in so many different aspects of care. Many people think that poison control only deals with kids or drug overdoses. It actually impacts all aspects of life and everything that you can potentially come into contact with on a daily basis. Outside of UPCC Mo is trying to learn to play golf, enjoys music, reading, cooking and she gardens. The gardening helps because many callers to UPCC call because of unknown plant exposures and it is easier to identify a plant when you spend a lot of time at a nursery.

**Thank You**

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.