Leslie R. Dye · Christine Murphy
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Aaron Skolnik *Editors*

Case Studies in Medical Toxicology

From the American College of Medical Toxicology

ACMT American College of Medical Toxicology
Medical Toxicology Foundation
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LD: For my husband, Brian, and my parents, Bernice and Ray—a perfect combination.

CM: Geoff, without your tolerance of the chaos around me, none of this would be possible. You are my rock.

DC: To my family, without whom nothing would be possible.

ML: This book is dedicated to my wife Ilene Claudius, and my parents Carol and Murray Levine.

AS: To the loves of my life, Jessica and Asher Lev.

Foreword

Medical toxicology, a specialty of medicine focused on the prevention, diagnosis, and management of human poisoning, is a discipline of stories. Unlike most illness, in which a disease insidiously overtakes a patient, poisoning is often a discrete, definable event. Viewed as a spectator, the event would appear as an unfolding series of foreseeable actions leading to an unintended culmination: poisoning. The child left alone with the bathroom cabinet ajar, the worker reaching for the "water bottle," the depressed patient attempting to end their anguish, the injection drug user buying from a new supplier, each representing a common scenario in which poisoning occurs. What happens next depends on many variables such as the nature, dose, and route of exposure, the size, age, and health of the patient, the set and setting, the recognition of the event, and even the availability and timely administration of the specific antidote.

Considering the many permutations, each of these unfolding stories requires skill to piece together in a logical and orderly manner. Prognosis guides expectation, and treatment quells fear. The knowledge and experience to understand the natural history of various poisonings are part of the early training necessary to become a medical toxicologist. This is a specialty of Sherlock Holmes-like detective work, in which no clues can be left untouched. Just as a single carbon separates an evening of gregarious enjoyment (ethanol) from a lifetime of blindness (methanol), no detail can be considered too small.

For several years, the American College of Medical Toxicology (ACMT), the professional organization of medical toxicologists, has held a monthly member-only, case-based webinar. During this time, I have led hundreds of participants on a journey to dissect complicated, intriguing human poisonings, while each shared their thoughts and beliefs on the how's and why's of medical management. Each case was initially selected for presentation because it was a challenge to someone, and on this basis it served as a learning tool for medical toxicologists across the USA and, often, across the world.

In this book, a group of dedicated medical toxicologists and gifted clinician educators have faithfully reproduced the case discussions, added detail, filled in blanks, and corrected errors, to allow others who were not able to engage in the initial

process to benefit from the work of the participants. The cases are anonymized, but nonetheless represent the potential for real life exposures that can, in an instant or over a decade, lead to consequential adverse effects on human health. To increase the value of the book, each case is followed by a discussion of key issues to broaden out the relevance to other medical specialties.

I want to thank the editors (Christina, Diane, Aaron, and Michael) for their tireless attention to detail. A particularly special thanks goes to the champion of the process, Leslie, for making this labor of love a reality. Hopefully their combined efforts will inspire the readers of the book to savor the intriguing tales, while reminding each of us about our tenuous relationship with the chemical milieu in which we live.

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Lewis S. Nelson

Preface

In 2011, the American College of Medical toxicology began offering webinars to members entitled, "National Case Conference." Real medical toxicology cases were presented by people from various training programs and were moderated by seasoned medical toxicologists. The popularity and educational value were quickly recognized and the webinars continue every month. The cases are usually presented by medical toxicology fellows, but sometimes also presented by residents or medical toxicologists who are faculty members. Listeners participate by asking and answering questions.

The format used produced valuable information that the editors thought would be an excellent foundation for a book of cases. Five prominent medical toxicologists, the lead editor an immediate past president of the American College of Medical Toxicology, edited all of the included cases. In addition, the editors added questions and answers that cover various aspects of medical toxicology, to allow readers to test their knowledge on a variety of toxicology topics. At the end of each case, specialty-specific guidance was added to broaden the appeal to providers in primary care and intensive care. This volume is a necessary resource for medical students, residents, and fellows, as well as seasoned medical providers.

Cincinnati, OH — Leslie R. Dye
Charlotte, NC — Christine Murphy
Newark, NJ — Diane P. Calello
Los Angeles, CA — Michael D. Levine
Pittsburgh, PA — Aaron Skolnik

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The editors would like to acknowledge the American College of Medical Toxicology, the organizers of the National Case Conference, and, most importantly, all of the patients and healthcare workers involved in these cases.

Disclaimer: NCC is an educational endeavor and a quality improvement effort intended to improve patient care. The cases in this book are not intended to define standard of care. Attempts have been made to ensure HIPAA compliance.

All data and information provided in this activity is for informational purposes only. The American College of Medical Toxicology and the editors and contributors of this book make no representations as to accuracy, completeness, present acceptability, suitability, or validity of the content and will not be liable for any errors or omissions in this information or any losses, injuries, or damages arising from its display or use.

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About the Editors

Leslie R. Dye, M.D., F.A.C.M.T. graduated from the University of Kansas School of Medicine and completed a residency in Emergency Medicine and fellowship in Medical Toxicology and Hyperbaric Medicine at the University of Cincinnati. She served as the Editor-in-Chief of the *Journal of Medical Toxicology*, has authored numerous book chapters, and has published extensively in the scientific literature. She currently serves as the Editor-in-Chief of Point of Care Content for Elsevier in addition to practicing addiction medicine. Dr. Dye is board certified in Emergency Medicine and Medical Toxicology and is the immediate past president of the American College of Medical Toxicology and the past president of the Medical Toxicology Foundation.

Christine Murphy, M.D. received both her bachelor's and master's degrees in chemistry from the College of William and Mary and her medical degree from the Medical College of Virginia. She completed her residency training in Emergency Medicine at Virginia Commonwealth University and a fellowship in Medical Toxicology at Carolinas Medical Center. She is currently an Assistant Professor at Carolinas Medical Center and Director of the Medical Toxicology Fellowship Program. Dr. Murphy is board certified in Emergency Medicine and Medical Toxicology. Her current interests include alternative uses for existing antidotes and trends in recreational drugs of abuse.

Diane P. Calello, M.D., F.A.C.M.T. is the Executive and Medical Director of the New Jersey Poison Information and Education System at the New Jersey Medical School of Rutgers University. She is also a member of the Board of Directors of the American College of Medical Toxicology and a regular contributor to the National Case Conference Webinar.She received her Bachelor of Arts from the College of William and Mary in Virginia and her medical degree from the New Jersey Medical School she now calls home. Her residency and fellowship training was conducted at the Children's Hospital of Philadelphia.She is board certified in Pediatrics, Pediatric Emergency Medicine,

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Michael D. Levine, M.D., F.A.C.M.T. After matriculating from the Chicago Medical School, Dr. Michael Levine completed an emergency medicine residency at the Brigham and Women's/Massachusetts General Hospital. He subsequently attended the Banner Good Samaritan Medical Center in Phoenix, Arizona, where he completed his medical toxicology fellowship. Michael Levine is currently faculty at the University of Southern California, where he serves as Chief of the Division of Medical Toxicology. His current research interests are mostly focused on toxicity from antiplatelets and anticoagulants. He is on the editorial board of the *Journal of Medical Toxicology*.

Aaron Skolnik, M.D. received his Medical Doctorate from the University of Pittsburgh School of Medicine and completed residency in emergency medicine at Brigham and Women's/Massachusetts General Hospital in Boston, MA. Thereafter, Aaron graduated from the medical toxicology fellowship at Banner Good Samaritan Medical Center in Phoenix, AZ, and joined the faculty of the University of Arizona College of Medicine, Phoenix. He is board certified in Emergency Medicine, Medical Toxicology, and Addiction Medicine. Currently, he is completing additional fellowship training at the University of Pittsburgh in critical care medicine, neurocritical care, and extracorporeal life support.

Case 1
Laundry Pod Ingestion in an Adult

1. Should we be concerned about laundry detergent (LD) pod exposures?
2. How are LD pods different from traditional LD products?
3. How should patients with LD pod exposures be managed?
4. What is being done to reduce harm from LD pod exposures?

Abstract Laundry detergent (LD) pod ingestion is an increasing source of morbidity and mortality in the pediatric population. However, injury associated with unintentional ingestions of LD pods by adults has not been described in the literature. We report a case of a 50-year-old man who ingested a LD pod and had esophageal and gastric injuries.

Keywords Laundry • Detergent • Pod • Caustics • Aspiration

Emergency Department Presentation

Chief Complaint: 50-year-old man presents with vomiting and odynophagia.

History of Present Illness

A 50-year-old hypertensive man who could not read English drank the contents of a Tide Pods® laundry detergent (LD) pod, mistaking it for candy. He vomited immediately after the ingestion and developed repeated emesis over the next 6 h. His

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efforts to eat and drink caused pain and repeated vomiting. The patient presented to ED 12 h after the ingestion, complaining of odynophagia.

Past Medical History	Hypertension
Medications	None
Allergies	None
Social History	Denied drinking alcohol, smoking cigarettes, and using illicit drugs

Physical Examination

Blood pressure	Heart rate	Respiratory rate	Temperature	O_2 saturation
185/111 mmHg	83 bpm	16 breaths/min	36.4 °C (97.6 °F)	97%

General: Lying in a gurney, comfortable
HEENT: Normocephalic with normal pupils, normal tongue, and oropharynx; no evidence of oropharyngeal burns
Cardiovascular: Regular rate and rhythm with no murmurs
Pulmonary: Symmetric breath sounds; lungs were clear to auscultation with no rales or rhonchi
Abdominal: Normal bowel sounds, soft, non-distended, and non-tender
Neurologic: Alert and oriented to person, place, and time; answered all questions appropriately
Skin: Warm and well-perfused

Diagnostic Testing

WBC	Hemoglobin	Hematocrit	Platelets
9.2 K/μL	15.2 g/dL	45%	223 K/dL

Na	K	Cl	CO_2	BUN	Cr	Glucose
139 mEq/L	4.0 mEq/L	103 mEq/L	27 mEq/L	16 mg/dL	0.8 mg/dL	98 mg/dL

Ancillary Testing

An esophagogastroduodenoscopy (EGD) performed in the ED revealed diffuse superficial erythema and ulcerations to the esophagus (Zargar's grade 2A) and stomach (Fig. A–D).

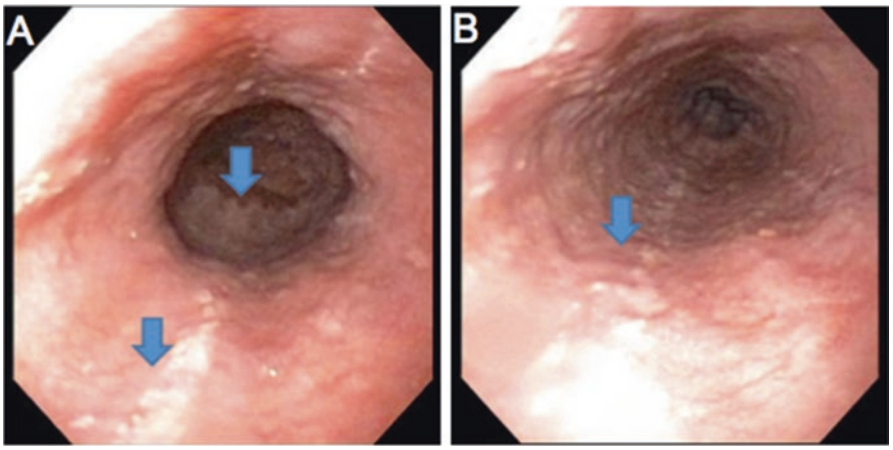

Fig. A, B Grade 2A esophageal injuries

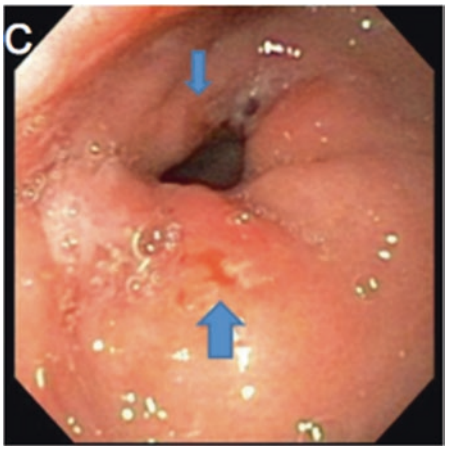

Fig. C Antral and pyloric ulcers

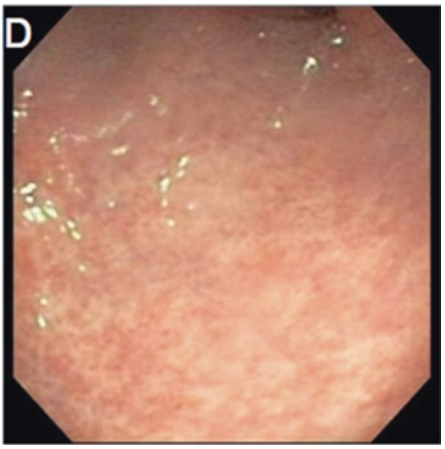

Fig. D Gastric mucosal erythema

Treatment and Hospital Course

The patient was managed with a proton pump inhibitor and given a liquid diet overnight. He had no further episodes of vomiting while in the hospital, and his odynophagia resolved. He was discharged the following day.

Key Points of Case

Should We Be Concerned About LD Pod Exposures?

In 2012, single-dose LD capsules emerged in the US market as a new, more convenient replacement for the liquid form. These colorful, attractive capsules can resemble candy or toys, likely playing an important role in the alarming number of pediatric exposures. From 2012 through 2103, poison control centers (PCC) in the US received over 17,000 calls reporting LD pod exposures in the pediatric population (Valdez et al. 2014). This astounding number represents less than 2 years of data collection and is likely an underrepresentation of the true exposure.

From 2012 through 2013, LD pod exposures required higher levels of care than pediatric exposures overall. (Valdez et al. 2014). Exposures in adults are much more uncommon. Pod exposures resulted in more than five times the serious outcomes compared to the traditional liquids and powders (Forrester 2013). A study looking into data from PCC recorded 102 children requiring tracheal intubation and two pediatric deaths associated with LD pod exposures (Valdez et al. 2014).

How Are LD Pods Different from Traditional Laundry Products?

Typically, unintentional ingestions of traditional detergent powders and liquids result in minimal toxicity; primarily gastrointestinal effects of mild mouth irritation and transient vomiting (Fulton 2011). The newer LD pod formulation has been available in Europe for a decade and has been associated with more significant morbidity. Although there are differences based on manufacturers, LD pods usually contain primarily ethoxylated alcohols, propylene glycol, and linear alkylbenzene sulfonate enclosed within a water-soluble polyvinyl alcohol membrane (Buehler et al. 2013).

LD pod ingestions result in many of the same gastrointestinal findings as their non-pod counterparts. However, pod ingestions appear to be associated with a greater degree of drowsiness/lethargy, coma, and loss of airway than ingestion of non-pod detergent formulations (Buehler et al. 2013; Forrester 2013). It is unclear

if these central effects are due to the ethoxylated alcohol or propylene glycol component, or both. It also remains unclear if exposed adults would share these similar neurologic findings.

How Should Patients with LD Pod Exposures Be Managed?

The initial management of LD pod ingestions is primarily supportive care.

Patients may or may not exhibit oropharyngeal irritation and burns, but as with other caustic exposures, these findings (or lack of) are not reliable predictors of esophageal and gastric injuries. Since there is no reliable relationship between oropharyngeal injuries and esophageal injuries, Crain et al. suggest that patients with a caustic exposure and two or more serious symptoms (vomiting, drooling, and stridor) should undergo endoscopy (Crain et al. 1984).

Studies looking specifically at esophageal injuries after LD pod ingestions are limited. The few case series and reports have found only superficial injury and none have reported any cases of esophageal strictures (Smith et al. 2014; Bramuzzo et al. 2013; Williams et al. 2012). Although the viscosity of the LD pod ingredients should limit its ability to cause distal injury, the ease of consuming larger quantities and the mode of delivery make injury difficult to predict. The decision to perform an EGD on patients who have ingested LD pods should depend on their presentation and progress.

What Is Being Done to Reduce Harm from LD Pod Exposures?

In May 2012, the American Association of Poison Control Centers sounded a nationwide alarm by issuing a release detailing safety precautions. Procter & Gamble (P&G), the maker of Tide Pods® LD pods, and other manufacturers responded with educational campaigns, appended warnings to its advertisements, and placed stickers on the container tubs to remind users to keep the products away from children. P&G has added latches to the lid of their product containers to make them harder to open (Ng 2013). They have also replaced the clear containers with opaque ones to decrease visibility to children.

The most recent data suggest that LD pod exposures may be on the decline; however, it is not yet clear if the decline is a result of harm reduction strategies or a seasonal trend in the number of PCC calls reporting exposures (Valdez et al. 2014). It is unknown whether the pod containers of any brand are truly child-resistant, and currently, there are no standards for safe packaging. Further research is needed to determine which components of the LD pods are most toxic. Once the most dangerous ingredients are determined, product reformulation may mitigate harm.

Specialty-Specific Guidance

Emergency Medicine

- Exposure to LD pods results in more severe adverse effects than exposure to traditional LD powders/liquids.
- Symptoms associated with LD pod include:
  - Gastrointestinal

    Vomiting
    Nausea
    Oropharyngeal irritation
    Abdominal pain
    Diarrhea
  - Neurologic

    Drowsiness
    Lethargy
    Agitation/irritability
    Coma
  - Pulmonary

    Coughing/choking
    Dyspnea
    Respiratory depression
    Pneumonitis
- Management
  - Management for LD pod ingestions is largely supportive
  - EGD according to clinical picture
  - Tracheal intubation when needed

Public Health

- Exposure to LD pods requires more medical attention, hospitalizations, and intensive care than exposures to traditional LD products.
- Public health efforts have resulted in a recent decrease in LD pod exposures, but safety standards still need to be established.
- Non-English speaking patients are at particular risk of poisoning, as the warnings on packaging of pharmaceuticals and hazardous materials can be missed.

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Case 2
Coma and Metabolic Acidosis

1. What common xenobiotics can cause metabolic acidosis?
2. What are common industrial settings or occupations that use the substance identified?
3. What are common industrial settings or occupations that use the substance identified?
4. What is the mechanism of action of the substance identified?
5. What is the role of laboratory testing for this substance?
6. What are the cardiovascular manifestations of the substance?
7. What are potential antidotes for this substance?
8. Which occupations use this substance routinely?

Abstract Cyanide is one of the few chemicals known as a "knock down" agent, owing to its short interval from ingestion until symptom onset. In this case, a 22-year-old female attempted suicide by consuming cyanide. This chapter discusses manifestations of cyanide, diagnostic clues, and management strategies for treating acute cyanide toxicity.

Keywords Suicide • Cyanide • Metabolic acidosis • Cyanide antidote • Hydroxycobalamin

History of Present Illness

Emergency Medical Services (EMS) was called to the home of a 22-year-old female who was found unresponsive. The patient had texted a friend a suicide message 15 min prior. When the friend was not able to get in contact with the patient, the friend called EMS. EMS arrived and found the patient unresponsive.

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Past Medical History	Depression
Medications	Fluoxetine
Allergies	No known drug allergies
Family History	Unknown
Social History	Unknown

Physical Examination

Blood pressure	Heart rate	Respiratory rate	Temperature	O_2 saturation
80/40 mmHg	120 bpm	24 breaths/min	37 °C (98.6 °F)	98% (room air)

A suicide note and a small canister of a product purchased on-line were found near the patient.

General: Unresponsive
Cardiovascular: Regular rhythm
Pulmonary: Lungs clear bilaterally
Neuro: Intact occulocephaic reflex with normal deep tendon reflexes. Muscle tone was normal, and there was no clonus. No response to pain.

Initial Treatment

The patient was placed on a non-rebreather mask and initial labs were obtained, including a blood gas. The patient was intubated, a head CT was obtained, and an antidote was administered.

Diagnostic Testing

WBC	Hemoglobin	Platelets
14 k/mm^3	12.5 g/dL	324 k/mm^3

Na	K	Cl	CO_2	BUN	Cr	Glucose
140 mmol/L	5.5 mmol/L	105 mmol/L	8 mmol/L	14 mg/dL	1.0 mg/dL	128 mg/dL

AST	ALT
68 IU/L	41 IU/L

Acetaminophen, salicylates, and ethanol were undetectable
Arterial blood gas (FiO2: 100%): pH 7.2; PCO2: 20; PO2: 270
CarboxyHgb: 2%; MetHtb: 1%
Venous blood gas (FiO2: 100%): pH 7.19; PCO2: 21; PO2: 267

Ancillary Testing

CT head: negative for hemorrhage or masses

What Common Xenobiotics Can Cause Metabolic Acidosis?

Common xenobiotics than can cause metabolic acidosis:

- Acetaminophen
- Acetazolamide
- Acetonitrile
- Azides
- Carbon monoxide
- Cyanide
- Didanosine
- Ethanol
- Ethylene glycol/diethylene glycol
- Ethylene glycol monobutyl ethers
- Formic acid
- Hydrogen cyanide
- Ketoacidosis (alcoholic, diabetic, etc.)
- Iron
- Isoniazid
- Metformin/phenformin
- Methanol
- Nitroprusside
- Phenol
- Phosphorus
- Propylene glycol
- Salicylates
- Theophylline
- Toluene
- Topiramate
- Valproic acid

What Are Common Industrial Settings or Occupations That Use Cyanide?

Common settings and occupations that use cyanide

- Chemical manufacturing
- Electroplating
- Jewelry making
- Laboratory work
- Metal polishing
- Metal plating
- Metal stripping
- Mirror manufacturing
- Nylon production
- Pesticide manufacturing

Hospital Course

Following antidote administration, the patient's hemodynamic status improved. The patient was admitted to the intensive care unit overnight and was discharged to inpatient psychiatry 2 days later.

What Is the Mechanism of Action of Cyanide?

Cyanide inhibits numerous enzymes, especially cytochrome oxidase (Ballantyne 1987). Other enzymes inhibited by cyanide include acetoacetate decarboxylase, carbonic anhydrase, glutamic acid decarboxylase, 2-keto-4-hydroglutarate aldolase, nitrite reductase, succinate dehydrogenase, and xanthine oxidase (Curry and LoVecchio 2001). In the inner mitochondrial membrane, cyanide binds to the ferric ion in cytochrome oxidase, thereby inhibiting electron transport. As a result, adenosine triphosphate (ATP) production is profoundly inhibited. Seizures may be the result of inhibition of glutamate decarboxylase, with a subsequent decrease in GABA concentrations. In addition, cyanide stimulates the NMDA receptor (Arden et al. 1998) and increases intracellular calcium (Mathangi and Namasivayam 2004), ultimately leading to apoptosis (Mills et al. 1996).

What Is the Role of Laboratory Testing for Cyanide?

Cyanide levels can be obtained at some institutions, but are typically only performed in specialized laboratories. The levels are technically difficult to run and rarely change management, owing to long time intervals between obtaining the test and the results. There are, however, several diagnostic clues that may facilitate the diagnosis of cyanide. In the appropriate clinical setting, a lactic acid exceeding 8 mmol/L (Baud et al. 2002) (and possibly 10 mmol/L) (Huzar et al. 2013), in conjunction with a partial pressure of oxygen <10 mmHg between venous and arterial blood, may suggest the diagnosis (Gracia and Shepherd 2004).

What Are the Cardiovascular Manifestations of Cyanide?

Because the heart is particularly sensitive to ATP depletion, it is one of the most affected organs in the body. Tachycardia, with or without mild hypertension, are early findings. Later, hypotension, bradycardia, and dysrhythmias may ensue. A shortening of the ST segment can occur, resulting in a "T on R" phenomenon (Brooks et al. 2011).

What Are Potential Antidotes for Cyanide?

There are two main potential treatments for cyanide toxicity.

Historically, treatment involves a commercially available cyanide antidote kit, which contains a combination of nitrites and thiosulfate. Amyl nitrite (which is available in an inhalational ampule) and sodium nitrite (which is available intravenously as a 3% solution) can induce methemoglobinemia (Chen and Rose 1952).

The sodium nitrite is responsible for the vast majority of the nitrite production. Sodium thiosulfate serves as a sulfur donor to the enzyme rhodinase, which helps convert cyanide to thiosulfate. The typical dose of sodium nitrite is 300 mg (10 cc of a 3% solution) for adults, or 0.33 cc/kg for pediatrics. A lower dose may be utilized in anemic patients. Sodium thiosulfate is made as a 25% solution; the typical adult dose is 12.5 g (50 cc), whereas the typical pediatric dose is 1.65 cc/kg.

In cases where cyanide toxicity is felt to be present concomitantly with carbon monoxide, as may be the case in a fire victim, nitrites should be avoided due to synergistic reduction in oxygen-carrying capacity between carboxyhemoglobin and methemoglobin (Levine and Spyres 2016).

Alternatively, hydroxocobalamin, a precursor to B_{12}, can be utilized. The cobalt ion on hydroxocobalamin combines with cyanide to form cyanocobalamin (B_{12}), which is renally eliminated. The typical starting dose of hydroxocobalamin is 5 g for adults; this dose can be repeated once. Because hydroxocobalamin can produce an intense red discoloration to body fluids, laboratory parameters which rely on colormetric testing, including liver functions, creatinine, and magnesium, can be difficult to interpret (Curry et al. 1994). There is some suggestion that administration of hydroxocobalamin along with sodium thiosulfate produces synergistic effects (Rose et al. 1965).

Cobalt EDTA, which has been used in Australia and parts of Europe, chelates cyanide. The complex is then excreted in the urine (Holland and Kozlowski 1986).

In addition to antidotal therapy, crystalloid fluid boluses and direct acting vasopressors can be utilized to treat hypotension.

Which Occupations Use Cyanide Routinely?

Jewelers and those involved with precious metal reclamation are some of the more common professions to utilize cyanide. Aqueous solutions of cyanide can combine with silver or gold to form soluble compounds. Copper mines frequently have large pools of aqueous, alkaline cyanide salts to facilitate the extraction of silver and gold from impure ore (Curry and LoVecchio 2001). Cyanide is also utilized in the production of paper, plastics, rubber, mirror making, and in electroplating operations. Historically, cyanide was commonly used in photography and fumigation. While firefighters do not typically work with cyanide directly, firefighters may be exposed from cyanide through smoke inhalation.

Speciality-Specific Guidance

Prehospital

In the event of possible cyanide gas, first responders should use appropriate personal protective equipment.

Emergency Medicine

The diagnosis of cyanide toxicity should be entertained if the history suggests a rapid "knock down."

The presence of similar PO2 between the venous and arterial blood, along with a markedly elevated lactic acid (usually greater than 10), suggests the diagnosis.

Patients with concurrent elevation of carboxyhemoglobin levels should not receive nitrites, as the simultaneous generation of methemoglobinemia can be dangerous.

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