88 Cyanide and Related Compounds—Sodium Azide

ALAN H. HALL, MD

At a Glance...

- Severe acute cyanide poisoning can be seen in a wide variety of settings, including enclosed-space fire smoke inhalation.
- Cyanide is a credible toxic terrorism threat agent.
- Whole-blood cyanide levels require several hours or longer to obtain.
- Emergent suspicion of the diagnosis and the decision to administer specific antidotes must be made on clinical and screening laboratory grounds.
- Elevated plasma lactate levels are a specific and sensitive indicator of the presence of significant cyanide poisoning in both smoke inhalation and pure cyanide poisoning cases.
- Several specific cyanide antidotes are available throughout the world.
- In the United States, only the cyanide antidote kit containing amyl nitrite for inhalation administration and sodium nitrite/sodium thiosulfate for intravenous administration is available as of June 2006.
- Amyl nitrite inhalation is an effective first-aid measure, especially in cases of hydrogen cyanide gas exposure.
- Growing evidence indicates that hydroxocobalamin may be the cyanide antidote of choice because of its efficacy and superior safety and adverse effects profile.
- The nitrite and thiosulfate antidote kit is not efficacious for sodium azide poisoning; hydroxocobalamin may be of theoretical benefit based on limited in vitro data.

INTRODUCTION AND RELEVANT HISTORY

Cyanide poisoning may be encountered in a wide variety of settings. Cyanide salts and hydrocyanic acid are used in common industrial processes such as electroplating, jewelry and metal cleaning, precious metal extraction, laboratory assays, and photographic processes.[1-4] Hydrogen cyanide is a chemical intermediate for the manufacture of synthetic fibers, plastics, and nitriles.[5] Criminal tampering by replacement of the ingredients in over-the-counter capsules with cyanide salts has resulted in a number of deaths.[6,7] Victims of enclosed-space fire-smoke inhalation may have both cyanide and carbon monoxide poisoning.[8,9]

Cyanide and carbon monoxide are synergistic toxicants[10] (see Chapters 86 and 87). Nontraumatic deaths in aircraft accidents may be due to inhalation of carbon monoxide and cyanide combustion products.[11] A number of compounds can liberate cyanide on spontaneous or thermal decomposition or by chemical reaction with acids (e.g., cyanogen, cyanogen bromide, cyanogen iodide, cyanogen chloride, calcium cyanide).[1] Cyanogen halides and hydrogen cyanide are potential chemical warfare agents.[12] At low concentrations, however, cyanogen halides are primarily lacrimating and pulmonary irritant agents.[3]

Cyanogenic compounds (laetrile, amygdalin from plant sources, nitrile compounds such as acetonitrile or propionitrile) can release cyanide during metabolism, chemical reaction in the gut, or bacterial degradation after ingestion.[3,13-17] Acute cyanide poisoning from apricot or peach kernels is unusual because the pits are usually swallowed whole and simply pass through the gastrointestinal tract; rare cases have been reported.[18] Severe or fatal cyanide poisoning with symptom onset delay of several hours has followed accidental acetonitrile ingestion from glue-on artificial nail–removing compounds.[19,20]

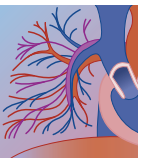
Acrylonitrile is a special case. After inhalation or dermal exposure, it both undergoes hepatic metabolism releasing cyanide and is itself hepatotoxic. Whole blood cyanide levels as high as 4.3 µg/mL have been found in patients with acrylonitrile poisoning.[17] In addition to supportive care and cyanide antidotes, treatment with *N*-acetylcysteine in a manner similar to that for acetaminophen poisoning has been recommended to prevent hepatotoxicity[17] (see Chapter 47).

Sodium nitroprusside releases cyanide during metabolism, which can result in elevated whole blood cyanide levels, and, occasionally, clinical cyanide poisoning.[21-24]

Coadministration of sodium thiosulfate or hydroxocobalamin can prevent cyanide toxicity, especially in patients receiving sodium nitroprusside infusions at rates greater than 2 µg/kg/minute[24,25] (see Chapter 61).

The frequent lack of correlation between blood cyanide levels and cyanide poisoning symptoms during nitroprusside administration suggests that the decision of whether to administer antidote therapy must be made on clinical grounds (e.g., presence of lactic acidosis or signs and symptoms consistent with cyanide poisoning). Clinical symptoms in this setting may, however, be due to thiocyanate accumulation.[26]

Chronic exposure to low levels of cyanide has been postulated to cause retrobulbar optic atrophy (in heavy smokers) and ataxic peripheral neuropathy (tropical ataxic neuropathy), as well as konzo (spastic upper motor neuron paraparesis) in people who consume large amounts of improperly prepared cassava, which contains the cyanogenic glycosides linamarin and lotaustralin in both roots and leaves.[27,28] Development of these neuropathies seems to require both chronic low-level cyanide exposure and either a deficiency of the endogenous cyanide-detoxifying enzyme rhodanese or protein-calorie malnutrition with dietary sulfur deficiency. A condition resembling acute cyanide poisoning treatable with hydroxocobalamin has resulted from acute ingestion of improperly prepared cassava.[29]



Mild disorders of vitamin B_{12} and folate levels and some subclinical thyroid function abnormalities were noted in one group of workers with chronic cyanide salt exposure.[2]

Thyroid enlargement (goiter) and altered iodine-131 uptake have also been described in workers chronically exposed to cyanide[3] and in populations eating an iodine-deficient monotonous cassava diet.[30]

EPIDEMIOLOGY

Despite widespread cyanide and cyanogenic compound use, serious acute cyanide poisoning is rare. Of a total of 2,267,979 human poison exposures reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS) during 2001, only 303 involved cyanide poisoning; of these, 17 were in children younger than 6 years of age, 17 were in patients 6 to 19 years of age, and 263 were in patients older than 19 years of age (the remainder were in patients of unknown age).[31]

Of the 295 cases in which the reason for exposure was known, 237 were unintentional exposures, 37 were intentional exposures, and 21 were classified as other.

A total of 199 (65%) of these patients were treated in a health care facility.[31] Of cyanide antidotes available in the United States, amyl nitrite was not listed in the 2001 TESS database, sodium nitrite administration was recorded in 27 instances, and sodium thiosulfate administration was recorded in 57 instances.

Of the 303 cyanide exposures, clinical outcome was known in only 194 (64%).[31] In 64 cases (21%), no signs or symptoms of cyanide poisoning developed; 116 patients (38%) became symptomatic, and 7 (2.3%) developed major symptoms (life-threatening signs or symptoms; significant residual disability or disfigurement).[31] Fourteen TESS-reported patients (4.6%) died of cyanide poisoning during 2001.[31]

Some details of these 14 fatal cyanide poisonings were available.[31] One involved combined carbon monoxide and cyanide poisoning from smoke inhalation (carboxyhemoglobin level, 35%; whole blood cyanide level, 40 µg/mL).

Of the 13 "pure" fatal cyanide poisoning cases, all were adults.[31] Ingestion of the involved cyanide compound was intentional in 12, and 1 case was classified as unintentional misuse. In three of these cases, whole blood cyanide levels were more than 20 µg/mL, 66 µg/mL, and 26.7 µg/mL; times after ingestion were not specified.

An adult man who worked in a jewelry shop drank from an already-open bottle of soda and rapidly developed fatal cardiac arrest. The soda was subsequently found to have a pH of 7 and a cyanide concentration of 100 mg/L.[31]

An elderly retired chemist accidentally ingested a swallow of sodium cyanide–copper cyanide etching solution. He was apparently successfully resuscitated from the initial severe cyanide poisoning, but subsequently developed fatal liver, renal, and pancreatic damage, suggesting that copper poisoning contributed to the fatal outcome.[31]

PHARMACOLOGY

Pathophysiology

Cyanide produces histotoxic hypoxia by binding with the ferric iron (Fe^{3+}) of mitochondrial cytochrome oxidase, thus disrupting the normal functioning of the electron transport chain and the ability of cells to utilize O_2 in oxidative phosphorylation.[1] The result is a shift to anaerobic metabolism, a substantial decrease in adenosine triphosphate synthesis, depletion of cellular energy stores, and greatly increased lactic acid production, which causes an elevated anion-gap metabolic acidosis. Numerous iron- or copper-containing enzymes are inhibited by cyanide, but cytochrome oxidase inhibition is the major intracellular toxic mechanism in cyanide poisoning.[3]

The tissue hypoxia of cyanide poisoning has several causes. Those tissues most dependent on oxidative phosphorylation—heart and brain—are the most severely and rapidly affected. Central inhibition of the respiratory centers leads to hypoventilation, which in turn produces hypoxic hypoxia.

Myocardial depression with decreased cardiac output produces stagnation hypoxia. Until the stage of respiratory depression or arrest, the blood is relatively normally oxygenated. However, the tissues are unable to extract and utilize this O_2, which leads to a greater than normal amount of O_2 in venous blood and an increased venous O_2 percent saturation.

Cyanide binding to cytochrome oxidase is a reversible process. The endogenous enzyme, rhodanese, is a natural defense against cyanide exposure. This enzyme complexes cyanide with sulfane sulfur, forming much less toxic thiocyanate. The body's sulfur pool is small, however, and the availability of sulfane sulfur constitutes the rate-limiting factor in natural cyanide detoxification. In the absence of an exogenous source of sulfur, rhodanese activity is too slow to prevent serious toxicity or death in significant cyanide poisoning.

The central nervous system is a primary target organ in cyanide poisoning.[32,33] The mechanism by which cyanide exposure causes neurotoxicity is not completely understood. An increase in intraneuronal calcium levels and lipid peroxidation, perhaps initiated by cyanide-induced decreased adenosine triphosphate levels, which impairs sodium and calcium extrusion processes, might be a mechanism of nerve injury.[34] Cyanide-induced apoptosis is mediated by cytochome-*c* release from mitochondria.[35] Generation of reactive oxygen species (ROS) also plays an important role in cyanide-induced apoptosis in cortical neurons.[33]

Pharmacokinetics

TOXICOKINETICS

The toxicokinetics of cyanide are not well understood. Available data are either from animal experiments or

anecdotal human case reports. In dog plasma in vitro, cyanide is about 60% protein bound.[36] In vivo, whole blood cyanide levels may be four or more times greater than serum levels because of the concentration of cyanide in erythrocytes.[1]

The volume of distribution (Vd) of cyanide in dogs is 0.498 L/kg.[37] A similar Vd of 0.41 L/kg was estimated in a single case of human potassium cyanide poisoning.[38] In this same case, estimates of other toxicokinetic parameters were area under the curve (AUC) 48 µg/mL/hr, clearance 163 mL/min, initial phase half-life ($t_{1/2\alpha}$) 20 to 30 minutes, and terminal-phase elimination half-life ($t_{1/2\beta}$) 19 hours.[38] The last value is consistent with findings in dogs showing only minimal excretion within the first 3 hours after oral administration, despite absorption of about 95%.[36] In victims of human cyanide poisoning from smoke inhalation, blood cyanide half-life was about 60 minutes.[9]

TOXICODYNAMICS

In a single patient not treated with specific antidotes, the average urinary cyanide excretion over nearly 40 hours was 0.64 mg/hr after a probable ingestion of between 117 and 511 mg of potassium cyanide.[6] In this same patient, the mean whole blood cyanide level 1 hour after ingestion was 8.2 µg/mL. This level increased to a mean of 19.7 µg/mL at 3 hours and to 23.4 µg/mL at 9 hours after ingestion. Despite intensive supportive treatment, this patient died about 40 hours after ingestion.

In contrast, in a patient who survived ingestion of 1 g of potassium cyanide after treatment with sodium nitrite and sodium thiosulfate, the highest whole blood cyanide level was 15.68 µg/mL at 1.75 hours after ingestion; this level decreased to 0.82 µg/mL at 5 hours after ingestion.[38] In another patient who survived cyanide poisoning secondary to dermal and inhalation exposure to propionitrile, treatment with hydroxocobalamin–sodium thiosulfate was associated with a decrease in the whole blood cyanide level from 5.71 µg/mL at 2 hours after exposure to 0.93 µg/mL 30 minutes later.[13] Specific cyanide antidote administration is associated with more rapid decreases in whole blood cyanide levels than is seen in patients not administered antidotes.[1]

TOXICOLOGY

Clinical Manifestations

The natural history of severe acute cyanide poisoning is a rapid progression (faster with inhalation than ingestion) to coma, shock, respiratory failure, and death.[1] Less severely poisoned patients administered only intensive supportive care have survived,[6,39] whereas patients also administered specific antidotes have survived with whole blood cyanide levels as high as 40 µg/mL.[40] Most patients who recover from acute cyanide poisoning do not have permanent sequelae, although rare cases of parkinsonian-like states with bilaterally symmetric lesions in the basal ganglia (putamen or globus pallidus) or memory deficits and personality changes have been reported.[16,41-43]

The clinical presentation depends on the route, dose, and time elapsed since exposure. Patients with inhalation exposure to high concentrations may experience sudden loss of consciousness after only a few breaths.[3,44] Combined inhalation and dermal or pure dermal exposure to a gas containing 19% hydrogen cyanide caused severe acute cyanide poisoning in two workers with whole blood cyanide levels of 5.3 and 6.75 µg/mL, respectively.[45] Patients who ingest potentially fatal amounts of cyanide salts may not develop life-threatening symptoms for up to 0.5 to 1 hour after exposure.[38] Delayed onset of symptoms (after 1 to 12 or more hours) may follow exposure to cyanogens such as laetrile, amygdalin, and nitrile compounds.[6,15,19,20]

In patients who do not experience sudden collapse, the initial signs and symptoms can resemble those of anxiety or hyperventilation.[1] Early signs include central nervous system stimulation (giddiness, headache, anxiety), tachycardia, hyperpnea, mild hypertension, and palpitations.[6]

Late signs are nausea, vomiting, tachycardia or bradycardia, hypotension, seizures (rare), coma, apnea, dilated pupils, and a variety of cardiac effects, including erratic supraventricular or ventricular arrhythmias, atrioventricular blocks, ischemic changes on electrocardiography, and asystole.[1] Noncardiogenic pulmonary edema may rarely occur, even after ingestion of cyanide salts.[39]

Of 21 acute cyanide poisoning victims, the following effects were noted: loss of consciousness (N = 15), metabolic acidosis (N = 14), cardiopulmonary failure (N = 9), anoxic encephalopathy (N = 6), and diabetes insipidus or conditions mimicking this condition (N = 1–3), which may be an ominous sign.[16]

The smell of "bitter almonds" (often described as "musty") may be appreciated in some cases, but the ability to detect this odor is genetically determined, and many people cannot do so.[1] Cyanosis is a late sign usually only noted at the stage of apnea and circulatory collapse.[1]

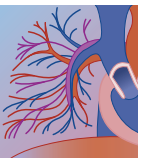
Dermal exposure to cyanide can result in systemic cyanide poisoning due to serious burns from molten cyanide salts, immersion in vats of cyanide salt solutions (with the potential for ingestion and vapor inhalation as well as dermal exposure), or total-body contamination with cyanide salts in confined spaces. Severe acute cyanide poisoning can rarely result from dermal exposure to hydrogen cyanide gas.[45]

Diagnosis

The initial physical examination focuses on the vital signs and the respiratory, cardiovascular, and central nervous systems. Continuous vital signs and electrocardiographic monitoring should be done. Whole blood cyanide levels are available, but generally take hours to obtain and cannot be used to guide emergent diagnosis or therapy.[1] They can, however, document the diagnosis and response to treatment.

LABORATORY TESTING

Plasma lactate, serum electrolytes, and arterial blood gases should be monitored as frequently as necessary to



guide fluid, electrolyte, sodium bicarbonate, and respiratory therapy. Pulse oximetry may be unreliable in cases of smoke inhalation with combined carbon monoxide and cyanide poisoning and after administration of methemoglobin-inducing cyanide antidotes.

Based on anecdotal case reports and animal experiments, certain screening laboratory values may help suggest the diagnosis when no history is available.[1] Cyanide produces lactic acidosis, which can be confirmed by plasma lactate measurements.[15,46] Normal plasma lactate levels are 1.0 mEq/L (mmol/L) or less. Lactic acidosis is present when serum lactate levels are more than 2.0 mEq/L (mmol/L). In combined poisoning with carbon monoxide and cyanide from smoke inhalation, plasma lactate levels may be the best marker of the presence and severity of a cyanide poisoning component.[9] Plasma lactate levels of 10 mEq/L (mmol/L) or greater in smoke inhalation victims without severe burns or levels of 8 mEq/L (mmol/L) or greater in patients with "pure" cyanide exposure are sensitive and specific indicators of cyanide poisoning.[47,48]

If the patient is still breathing or is receiving assisted ventilation, the arterial partial pressure of O_2 may be relatively normal. Cyanide inhibits the extraction of O_2 from the blood at the tissue level. Thus, more O_2 than normal is present in the venous blood; this may be reflected by an increased (>40 mm Hg) peripheral venous partial pressure of O_2, an increased measured peripheral venous O_2 percent saturation (>70%), or a narrowing of the normal difference between the measured arterial O_2 percent saturation and the measured central venous or pulmonary artery O_2 percent saturation (the normal central venous O_2 percent saturation is about 70%).[1,16] However, a mixed venous O_2 percent saturation less than 90% does not, in itself, exclude acute cyanide poisoning.[15]

OTHER DIAGNOSTIC TESTING

If pulmonary edema develops, a chest radiograph should be obtained periodically.

A smoke inhalation clinical scoring system (scale from 1 to 10) based on the following clinical findings has been proposed: hoarseness (1 point); stridor (1 point); carbonaceous sputum (1 point); soot in the airways (1 point); singed nasal hairs (1 point); facial burns (1 point); abnormal chest auscultation findings (1 point); mental status change (1 point); and abnormal findings on chest radiography (2 points). In one case series, this clinical scoring system was predictive of a fatal outcome after smoke inhalation exposure from enclosed-space fires; it was also the strongest predictor of measured carboxyhemoglobin and whole blood cyanide levels.[49]

DIFFERENTIAL DIAGNOSIS

Other cytochrome oxidase inhibitors such as hydrogen sulfide and sodium azide may produce clinical and laboratory findings similar to those seen in cyanide poisoning (see Chapter 91 and later discussion in this chapter on Sodium Azide). Although sodium nitrite might have some efficacy in the treatment of hydrogen sulfide poisoning, it is ineffective for treating sodium azide poisoning.[50]

MANAGEMENT

Supportive Measures

Cyanide-exposed patients with only restlessness, anxiety, or hyperventilation do not require antidote therapy. Such patients should be administered supplemental O_2 and undergo a few hours of clinical monitoring. Antidotes should be administered only if more serious symptoms develop.

Rescuers must not enter areas with high airborne concentrations of cyanide without a self-contained breathing apparatus or air-supplied respirators. Mouth-to-mouth breathing should be avoided if at all possible, and care must be taken by rescuers not to inhale the victim's exhaled breath. Appropriate prehospital care consists of airway management, including endotracheal intubation if required, administration of 100% supplemental O_2 by tight-fitting mask or endotracheal tube, placement of at least one large-bore intravenous line, administration of sodium bicarbonate if shock (with presumed metabolic acidosis) is present, decontamination of exposed skin or eyes, administration of standard antiarrhythmic or anticonvulsant medications if necessary, and administration of amyl nitrite by inhalation.

Amyl nitrite pearls may be broken in gauze and held close to the nose and mouth of patients who are spontaneously breathing. Alternatively, they may be placed into the lip of the facemask or inside the resuscitation bag in patients with apnea or hypoventilation. Amyl nitrite should be inhaled for 30 seconds of each minute, and a used pearl should be replaced with a fresh one every 3 to 4 minutes. Amyl nitrite and supplemental O_2 administration alone have been efficacious in treating hydrogen cyanide–poisoned patients in one occupational exposure setting.[51] Supportive measures alone may sometimes prove to be satisfactory,[39,44] although patients administered specific antidotes together with supportive therapy have survived with higher whole blood cyanide levels, awakened sooner from coma, and had more rapid resolution of acidosis.[6,38,39]

Standard antiarrhythmic and anticonvulsant medications are appropriate for the treatment of cyanide-induced arrhythmias and seizures. Atropine or vasopressors may be required if symptomatic bradycardia or hypotension unresponsive to less aggressive measures are present.

Normobaric O_2 is synergistic with cyanide antidotes. Although not proved, hyperbaric oxygen (HBO) may be efficacious in patients not responsive to supportive and antidotal therapy, and some severely cyanide-poisoned patients treated with HBO have survived.[14,46] Smoke inhalation victims with serious known carbon monoxide poisoning and suspected cyanide toxicity may be treated with HBO when available.[8]

Decontamination

Exposed skin and eyes should be copiously flushed with water or normal saline. Contaminated clothing should be removed and isolated in impervious containers. Inducing emesis is contraindicated because of the potential for rapid progression to coma or seizures. Gastric aspiration might be beneficial within about 30 minutes after ingestion of cyanide salts. Although older references question the efficacy of activated charcoal administration, a single dose of about 1 g of activated charcoal per kilogram of body weight may be administered to patients who have ingested cyanide salts and related compounds.

Antidotes

In the United States and some other countries, specific therapy consists of the administration of the antidotes found in the cyanide antidote kit. Once intravenous access has been established, amyl nitrite inhalation should be discontinued and sodium nitrite administered intravenously. The usual adult dose is 300 mg (one 10-mL ampoule of 3% solution). The pediatric dose for the average child is 0.12 to 0.33 mL/kg administered over absolutely no less than 5 minutes intravenously.

Sodium nitrite is a potent vasodilator, and rapid administration may cause significant hypotension, which can be avoided by initial slow administration, either (1) by slow intravenous push over absolutely no less than 5 minutes, or (2) by diluting the dose in 50 to 100 mL of 5% dextrose in water, initially beginning with a slow infusion rate, and then increasing to the most rapid rate possible without causing hypotension. Frequent blood pressure monitoring should be done during sodium nitrite administration.

Another potentially serious, although rare, adverse effect of sodium nitrite administration is induction of excessive methemoglobin levels. Induction of some level of methemoglobinemia has long been thought to be the mechanism of action of sodium nitrite because methemoglobin has a greater affinity for cyanide than cytochrome oxidase. This hypothesis has been questioned.

Excessive methemoglobin induction occurs most often in patients given excessive amounts of sodium nitrite, but it is rarely seen with therapeutic doses. Methemoglobin levels should be monitored, especially when multiple doses of sodium nitrite are required. Inducing levels greater than 30% to 40% must be avoided. The determinant of when "enough" sodium nitrite has been infused is the patient's clinical response.

Sodium nitrite is followed by intravenous administration of sodium thiosulfate, in an adult dose of 12.5 g (one 50-mL ampoule of a 25% solution). The average pediatric dose is 1.65 mL/kg. No cases of significant adverse effects from sodium thiosulfate administration have been reported in humans, despite more than 50 years of clinical use of the drug. A continuous infusion of 1 g of sodium thiosulfate per hour for 24 hours was considered efficacious in one case of potassium cyanide ingestion poisoning.[52]

In cases of smoke inhalation with known carbon monoxide and suspected cyanide poisoning, sodium thiosulfate and 100% supplemental O_2 can be administered initially if hydroxocobalamin is not available. Sodium nitrite administration should be withheld until the patient is at pressure in an HBO chamber, where dissolved plasma O_2 can adequately compensate for induced methemoglobinemia.[8] When HBO was not immediately available for treatment of smoke inhalation patients, sodium nitrite was administered successfully without significant complications.[53]

Second doses of sodium nitrite and sodium thiosulfate at one half the initial amounts may be administered 30 minutes after the first doses if clinical response is inadequate. With exposure to certain nitrile compounds, continued metabolic release of cyanide may cause prolonged poisoning requiring multiple antidote doses. If producing a satisfactory clinical response, sodium thiosulfate alone could be used in such cases because its inherent toxicity is low.

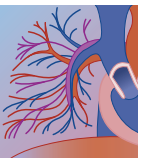
Alternate antidotes in clinical use in other parts of the world such as hydroxocobalamin (Cyanokit), dicobalt–ethylenediaminetetra-acetic acid (Kelocyanor), and 4-dimethylaminophenol (4-DMAP) are not available in the United States as of June 2006. A growing body of evidence, primarily from patients with combined carbon monoxide and cyanide poisoning from enclosed-space fire smoke inhalation, but also from patients with aliphatic nitrile or cyanide salt poisoning, indicates that hydroxocobalamin may be the cyanide antidote of choice.[47,54,55]

Hydroxocobalamin is more rapidly acting than sodium thiosulfate, does not produce methemoglobinemia, which can impair oxygen transport as do 4-DMAP and the nitrites, does not cause hypotension as does sodium nitrite, and has a much better adverse effect and safety profile than do the nitrites, 4-DMAP and Kelocyanor.[47,54] It has been shown to be safe and effective for decreasing low whole blood cyanide levels in volunteer heavy smokers and is an effective and safe cyanide antidote in a variety of experimental animal species.[56,57] The only noted side effect in patients treated with hydroxocobalamin has been transient reddish-brown discoloration of the urine, sclera, mucous membranes, and skin from the color of the medication itself.[47,54] Hydrocobalamin can be combined with sodium thiosulfate in more severe poisoning cases because there is an antidotal synergy.[47,54,57]

Because of its intense reddish-brown color and peak light absorption at 352 and 525 nm, hydroxocobalamin can interfere with automated colorimetric clinical chemistry measurements of aspartate aminotransferase, total bilirubin, creatinine, magnesium, and serum iron.[58]

Elimination

Hemodialysis cannot be considered standard treatment for cyanide poisoning, but it has been efficaciously used as supportive therapy in a patient who developed renal failure secondary to rhabdomyolysis in the course of severe cyanide poisoning.[16] One patient with severe acute



cyanide poisoning treated with supportive measures, antidotes, and charcoal hemoperfusion has also been reported.[4] This patient was improving after antidotal and supportive therapy at the time that hemoperfusion was begun. Hemoperfusion has no place in the treatment of acute cyanide poisoning.

Disposition

Asymptomatic patients with apparent minimal exposure should be observed in a controlled setting for 4 to 6 hours. If exposure was to a nitrile compound, the onset of symptoms may be delayed for 12 hours or longer; in this situation, a longer period of observation and monitoring is necessary.

Patients who have serious symptoms (coma, seizures, shock, metabolic acidosis, cardiac arrhythmias, ischemic electrocardiographic changes, or hypoventilation) and all those administered antidotes should be admitted to an intensive care unit for clinical monitoring until all symptoms have resolved, or for a minimum period of 24 hours. Outpatient follow-up at intervals for a period of weeks should be arranged to screen for the possible development of rare delayed central nervous system effects.

Given the acute shortage of suitable organ donors, brain-dead poisoning victims should not be excluded as donors, if: (1) clinical and laboratory evidence shows true brain death (*not* central nervous system depression or lack of central nervous system activity due to the continued presence of the poison); (2) the poison itself has not irretrievably damaged or destroyed the organ under consideration for transplantation; and (3) the organ being considered for transplantation is not a reservoir, such that the transplanted organ itself might secondarily poison the transplant recipient. Organs have been successfully transplanted from brain-dead acute cyanide poisoning victims without causing secondary cyanide poisoning.[59,60]

SODIUM AZIDE

Sodium azide is a white to colorless crystalline solid that is highly soluble in water and is used as a preservative in aqueous laboratory reagents and biologic fluids and in automobile airbags as a gas generator.[61] It has also been investigated for use as an herbicide, insecticide, nematocide, fungicide, and bacteriocide and is used in the manufacturing of rubber, latex, wine, and Japanese beer, and as a chemical intermediate in lead azide production.[61] Its use in automotive airbags has not resulted in sodium azide poisoning, but it has rarely caused relatively minor chemical burns by producing nitrogen gas and sodium oxide; the latter reacts with water to form corrosive sodium hydroxide.[61]

Sodium azide poisoning has most often occurred as a result of accidental or suicidal ingestion of colorless, odorless, tasteless laboratory solutions, which can be mistaken for water or normal saline, and has occurred in health care settings or laboratories.[61–63] Suicidal cases have generally been seen in individuals with access to the chemical in laboratories because otherwise it has limited availability.[63,64] One patient died after mistakenly ingesting 1 g of sodium azide obtained from a hospital but intended to be added as a preservative to a container for his 24-hour urine specimen.[65]

The 2001 American Association of Poison Control Centers TESS[31] does not have a specific listing for sodium azide. A recent systematic review covering the period of 1927 to 1999 found that a total of 38 publications constituted the knowledge base of sodium azide human health effects.[61] Of these, 32 publications were case reports, 5 were occupational studies, and 1 paper was an experimental study of the use of sodium azide as a potential antihypertensive agent (since abandoned because of significant side effects).[61,64] There were a total of 185 exposed people, with 116 from the experimental study.[61] Adults were involved in 183 cases and children in 2 cases.

Of the 69 acute poisoning cases, 43 followed ingestion (26 survivors; 17 fatalities), 12 followed inhalation from occupational exposure (all 12 patients survived), 9 were exposed by the intravenous route from sodium azide contamination of hemodialysis apparatus (all 9 survived), and 5 patients had dermal exposure (4 survivors; 1 fatality).[61] The dermal exposure fatality involved exposure to a metal azide during an explosion causing 45% total-body surface area burns.[61] The hemodialysis patients exposed by the intravenous route developed hypotension, blurred vision, headache, nausea, vomiting, syncope, and cramping when ultrafilters used for preparation of dialysis fluid were pretreated with a preservative consisting of 0.25% sodium azide and 25% glycerin and not flushed.[66]

Ingestion is the most common route of exposure in serious poisoning cases.[61] Fatality is usually associated with doses greater than 700 mg (or 10–13 mg/kg), whereas nonfatal poisoning has been seen with doses ranging from 0.3 to 150 mg (or 0.004–2 mg/kg).[61] In a series of four fatal and six nonfatal sodium azide poisoning cases, the lowest dose in survivors was 5 to 10 mg, and the highest dose was 80 mg.[67] The lowest fatal doses were 0.7 g in women and 1.2 to 2 g in men.[67]

Sodium azide is rapidly absorbed from the gastrointestinal and respiratory tracts (as hydroazoic acid vapor).[61] Its extent of dermal absorption is unclear, but a single fatal case from a warehouse accident has been reported.[61] Sodium azide is metabolized by the liver and excreted by the kidneys, but human absorption, distribution, metabolism, and excretion kinetics data are not available,[61] except for a half-life of about 2.5 hours calculated in a single fatal case.[68]

Hypotension is the most common clinical effect, and the time between exposure and the onset of hypotension is somewhat predictive of survival.[61] When hypotension occurs within minutes to 1 hour after exposure, it is a physiologic response, and the clinical course is most often benign. When the hypotension is delayed in onset more than 1 hour, it ". . . constitutes an ominous sign for death."[61]

Other common clinical effects are nausea, vomiting, diarrhea, headache, dizziness, temporary vision loss, pal-

pitations, dyspnea, temporary loss of consciousness, and depressed sensorium.[61] Markedly depressed sensorium, seizures, coma, hypothermia, cardiac dysrhythmias, chest pain, tachypnea, cyanosis, noncardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), metabolic acidosis, oliguria, and cardiorespiratory arrest are seen in severe poisoning cases.[61,62,65,68]

The hypotensive effects are due to dilation of peripheral blood vessels, but it is unclear whether this effect is caused by the parent compound or its metabolism to nitric oxide.[61] Sodium azide does inhibit heme-containing enzymes such as catalase, peroxidase, and cytochrome oxidase,[61,69,70] but its lethality may be due instead to enhanced excitatory nervous transmission in the central nervous system, caused by the parent compound itself or by metabolically released nitric oxide.[61,71]

One case of cardiomyopathy presenting as an acute myocardial infarction was reported in a previously healthy 29-year-old female student who mistakenly ingested 700 mL of a buffering solution containing 0.1% sodium azide.[72] Nausea, weakness, and confusion occurred initially and prompted overnight observation in a hospital. These effects had resolved by the following morning, and she was discharged, only to develop exertional dyspnea over the following 24 hours and severe precordial chest pain radiating to the left arm 3 days after ingestion. Electrocardiogram and creatine kinase elevations indicated possible myocardial infarction. Cardiac catheterization and chest x-ray were consistent with cardiomyopathy. Over several hours, the patient developed episodes of ventricular tachycardia and refractory hypotension and died in asystolic arrest. At autopsy, histology of the left ventricle revealed cardiomyopathy but no monocellular infiltrates to suggest an inflammatory etiology.[72] Chest pain for 6 months after survival of acute sodium azide poisoning has been reported in one patient who ingested 80 mg.[67]

Sodium azide levels in blood are not readily available, and diagnosis and treatment decisions must be based on clinical grounds. Postmortem blood concentrations have ranged from 7.4 to 8.3 mg/L in one acutely fatal suicidal case to between 40 and 262 mg/L in other reported cases.[64] Interestingly, cyanide has been detected in the postmortem blood in three sodium azide fatalities (0.38 mg/L, 1.6 mg/L, and 9 mg/L), but it is not clear whether the cyanide production took place in vivo or in the postmortem remains.[64]

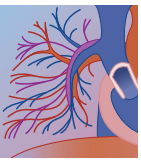
Severe hypotension may be unresponsive to volume expansion and vasopressors.[61] Phenobarbital had a protective effect against sodium azide poisoning in mice and rats, whereas diazepam and phenytoin did not.[71] Phenobarbital should thus be considered for patients with seizures after sodium azide exposure not responsive to other anticonvulsants.

There is no specific antidote for sodium azide poisoning in current clinical use[61,72] and only symptomatic and supportive treatment can be given.[63] The U.S. cyanide antidote kit containing amyl nitrite, sodium nitrite, and sodium thiosulfate has not been efficacious in human poisoning cases or in animal experiments.[61,67,71,73] Kelocyanor (dicobalt EDTA) and sodium thiosulfate alone have been ineffective for prevention of sodium azide poisoning in experimental animals.[71]

Hydroxocobalamin has not been administered to sodium azide–poisoned humans. An in vitro study in isolated rat mitochondria found that when hydroxocobalamin was added to sodium azide–inhibited mitochondria, cytochrome-*c* oxidase was less inhibited than when sodium azide was added alone.[74] This gives a potential theoretical mechanism of action for hydrocobalamin in the treatment of sodium azide poisoning, and further studies should be pursued. When it is available, hydroxocobalamin could be administered to patients with life-threatening sodium azide poisoning because of its highly favorable safety profile. It is notably efficacious for reversing the severe hypotension seen in acute cyanide poisoning, and severe hypotension unresponsive to usual treatments is a hallmark of sodium azide poisoning.

REFERENCES

1. Hall AH, Rumack BH: Clinical toxicology of cyanide. Ann Emerg Med 1986;15:1067.
2. Blanc P, Hogan M, Mallin K, et al: Cyanide intoxication among silver-reclaiming workers. JAMA 1985;253:367.
3. Hartung R: Cyanides and nitriles. In Clayton GD, Clayton FE (eds): Patty's Industrial Hygiene and Toxicology, Vol. 11, 4th ed. New York, John Wiley, 1994, p 3119.
4. Krieg A, Saxena K: Cyanide poisoning from metal cleaning solutions. Ann Emerg Med 1987;16:582.
5. Hathaway GJ, Proctor NH, Hughes JP: Hydrogen cyanide. In Proctor and Hughes' Chemical Hazards of the Workplace, 4th ed. New York, Van Nostrand Reinhold, 1996, p 346.
6. Hall AH, Rumack BH, Schaffer MI, Linden CH: Clinical toxicology of cyanide: North American clinical experiences. In Ballantyne B, Marrs TC (eds): Clinical and Experimental Toxicology of Cyanides. Bristol, UK, John Wright, 1987, p 312.
7. Anonymous: Cyanide poisoning associated with over-the-counter medication—Washington State. MMWR Morb Mortal Wkly Rep 1991;40:161.
8. Hart GB, Strauss MB, Lennon PA, Whitcraft DD: Treatment of smoke inhalation by hyperbaric oxygen. J Emerg Med 1985;3:211.
9. Baud FJ, Barriot P, Toffis V, et al: Elevated blood cyanide concentrations in victims of smoke inhalation. N Engl J Med 1991;325:1761.
10. Norris JC, Moore SJ, Hume AS: Synergistic lethality induced by the combination of carbon monoxide and cyanide. Toxicology 1986;40:121.
11. Mayes RW: The toxicological examination of the British Air Tours Boeing 737 accident at Manchester in 1985. J Forensic Sci 1991;36:179.
12. Barr SJ: Chemical warfare agents. Top Emerg Med 1985;7:62.
13. Bismuth C, Baud FJ, Djeghout H, et al: Cyanide poisoning from propionitrile exposure. J Emerg Med 1987;5:191.
14. Scolnik B, Hamel D, Woolf AD: Successful treatment of life-threatening propionitrile exposure with sodium nitrite/sodium thiosulfate followed by hyperbaric oxygen. J Occup Med 1993; 35:577.
15. Yeh MM, Becker CE, Arieff AI: Is measurement of venous oxygen saturation useful in the diagnosis of cyanide poisoning? Am J Med 1992;93:582.
16. Yen D, Tsai J, Wang L-M, et al: The clinical experience of acute cyanide poisoning. Am J Emerg Med 1995;13:524.
17. Peden NR, Taha A, McSorley PD, et al: Industrial exposure to hydrogen cyanide: implications for treatment. BMJ 1986;293:538.
18. Suchard JR, Wallace WL, Gerkin RD: Acute cyanide poisoning caused by apricot kernel ingestion. Ann Emerg Med 1998;32:724.
19. Kurt TH, Day LC, Reed WG: Cyanide poisoning from glue-on nail remover. Am J Emerg Med 1991;9:201.



20. Michaelis HC, Clemens C, Kijewski H, et al: Acetonitrile concentrations and cyanide levels in a case of suicidal oral acetonitrile ingestion. J Toxicol Clin Toxicol 1991;29:447.
21. Schulz V, Gross R, Pasch T, et al: Cyanide toxicity of sodium nitroprusside in therapeutic use with and without sodium thiosulfate. Klin Wochenschr 1982;60:1393.
22. Linakis JG, Lacouture PG, Woolf A: Monitoring cyanide and thiocyanate concentrations during infusion of sodium nitroprusside in children. Pediatr Cardiol 1991;12:214.
23. Vesey CJ, Cole PV, Linnell JC, Wilson J: Some metabolic effects of sodium nitroprusside in man. BMJ 1974;2:140.
24. Cottrell JE, Casthely P, Brodie JD, et al: Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 1978;298:809.
25. Vesey CJ, Cole PV: Blood cyanide and thiocyanate concentrations produced by long-term therapy with sodium nitroprusside. Br J Anaesthiol 1985;57:148.
26. Osuntokun BO: Chronic cyanide intoxication of dietary origin and a degenerative neuropathy in Nigerians. Acta Hortic 1994;375:311.
27. Tylleskar T, Howlett WP, Rwiza HT, et al: Konzo: a distinct disease entity with selective upper motor neuron damage. J Neurol Neurosurg Psychiatr 1993;56:638.
28. Ngudi DD, Kuo YH, Lambein F: Cassava cyanogens and free amino acids in raw and cooked cassava leaves. Food Chem Toxicol 2003;41:1193.
29. Espinoza OB, Perez M, Ramirez MS: Bitter cassava poisoning in eight children: a case report. Vet Hum Toxicol 1992;34:65.
30. Delange F, Ekpechi LO, Rosling H: Cassava cyanogenesis and iodine deficiency disorders. Acta Hortic 1994;375:289.
31. Litovitz TL, Klein-Schwartz W, Rodgers GC, et al: 2001 annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2002;20:391.
32. Shou Y, Gunasekar PG, Borowitz JL, et al: Cyanide-induced apoptosis involves oxidative-stress-activated NF-kappaB in cortical neurons. Toxicol Appl Pharmacol 2000;164:196.
33. Bi QN, Sun PW, Gunasekar PG, Isom GE: Involvement of CA^{2+}/calmodulin-dependent protein kinase II in cyanide-induced cytotoxicity in cultured cerebellar granular cells [abstract]. Toxicologist 1996;30:186.
34. Shou Y, Li L, Prabhakaran K, et al: p38 Mitogen activated protein kinase regulates BAX translocation in cyanide-induced apoptosis. Toxicol Sci 2003;75:99.
35. Christel D, Eyer P, Hegemann M, et al: Pharmacokinetics of cyanide poisoning in dogs, and the effects of 4-dimethylaminophenol or thiosulfate. Arch Toxicol 1977;38:177.
36. Sylvester DM, Hayton WL, Morgan RL, Way JL: Effects of thiosulfate on cyanide pharmacokinetics in dogs. Toxicol Appl Pharmacol 1983;69:265.
37. Hall AH, Doutre WH, Ludden T, et al: Nitrite/thiosulfate treated acute cyanide poisoning: estimated kinetics after antidote. Clin Toxicol 1987;25:121.
38. Graham DL, Laman D, Theodore J, Robin ED: Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. Arch Intern Med 1977;137:1051.
39. Feihl F, Domenighetti G, Perret C: Intoxication massive au cyanure avec evolution favorable. Schweiz Med Wschr 1982;112:1280.
40. Jouglard J, Fagot G, Deguigne B, Arlaud J-A: L'intoxication cyanhydrique aigue et son traitement d'urgence. Mars Med 1971;9:571.
41. Rosenberg NL, Myes JA, Martin MRW: Cyanide-induced parkinsonism: clinical, MRI, and 6-fluorodopa PET studies. Neurology 1989;39:142.
42. Feldman JM, Feldman MD: Sequelae of attempted suicide by cyanide ingestion: a case report. Int J Psychiatr Med 1990;20:173.
43. Steffens W, Leng G, Bayer KB: Nitrile poisonings: cyanide formation, clinical course and treatment [abstract]. J Toxicol Clin Toxicol 2003;41:410.
44. Steffens W, Leng G, Pelster M: Percutaneous hydrocyanic acid poisoning [abstract]. J Toxicol Clin Toxicol 2003;41:483.
45. Goodhart GL: Patient treated with antidote kit and hyperbaric oxygen survives cyanide poisoning. South Med J 1994;87:814.
46. Megarbane B, Delahaye A, Goldgran-Toledano D, et al: Antidotal treatment of cyanide poisoning. J Chin Med Assoc 2003;66:193.
47. Baud FJ, Borron SW, Megarbane B, et al: Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. Crit Care Med 2002;30:2044.
48. Shusterman D, Alexeef G, Hargis C, et al: Predictors of carbon monoxide and hydrogen cyanide exposure in smoke inhalation patients. Clin Toxicol 1996;34:61.
49. Hall AH, Rumack BH: Hydrogen sulfide poisoning: an antidotal role for sodium nitrite? Vet Human Toxicol 1997;39:152.
50. Wurzburg H: Treatment of cyanide poisoning in an industrial setting. Vet Hum Toxicol 1996;38:44.
51. Heintz B, Bock TA, Kierdorf H, Sieberth HG: Cyanid Intoxikation: Behandlung mit Hyperoxigenation und Natriumthiosulfat. Dtsch Med Wochenschr 1990;115:1100.
52. Kirk MA, Gerace R, Kulig KW: Cyanide and methemoglobin kinetics in smoke inhalation victims treated with the cyanide antidote kit. Ann Emerg Med 1993;22:9.
53. Megarbane B, Baud F: Cyanide poisoning: diagnosis and antidote choice in an emergency situation [abstract]. J Toxicol Clin Toxicol 2003;41:438.
54. Santiago I: [Gas poisoning]. An Sist Sanit Navar 2003;26(Suppl 1):173.
55. Suchard JR, Wallace KL, Gerkin RD: Acute cyanide toxicity caused by apricot kernal ingestion. Ann Emerg Med 1998;32:724.
56. Forsyth JC, Mueller PD, Becker CE, et al: Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. J Toxicol Clin Toxicol 1993;31:277.
57. Hall AH, Rumack BH: Hydroxycobalamin as a cyanide antidote. J Emerg Med 1987;5:115.
58. Curry SC, Connor DA, Rashke RA: Effect of the cyanide antidote hydroxocobalamin on commonly ordered serum chemistry studies. Ann Emerg Med 1994;24:65.
59. Swanson-Bierman B, Krenzelok EP, Snyder JW, et al: Successful donation and transplantation of multiple organs from a victim of cyanide poisoning. Clin Toxicol 1993;31:95.
60. Hantson P, Mahieu P, Hassoun A, Otte J-B: Outcome following organ removal from poisoned donors in brain death status: a report of 12 cases and review of the literature. Clin Toxicol 1995;33:709.
61. Chang S, Lamm SH: Human health effects of sodium azide exposure: a literature review and analysis. Int J Toxicol 2003;22:175.
62. Singh N, Singh CP, Brar CK: Sodium azide: a rare poisoning. J Assoc Physicians India 1994;42:755.
63. Wollenek G: Akute vergiftungen durch natriumazid. Wein Klin Wochenschr 1989;101:314.
64. Marquet P, Clément S, Lotfi H, et al: Analytical findings in a suicide involving sodium azide. J Anal Toxicol 1996;20:134.
65. Herbold M, Schmitt G, Aderjan R, Pedal I: Tödliche natriumazidvergiftung im krankenhaus: eine vermeidbarer zwischenfall. Arch Kriminol 1995;196:143.
66. Arduino MJ: CDC investigations of noninfectious outbreaks of adverse events in hemodialysis facilities, 1979–1999. Semin Dial 2000;13:86.
67. Chiba M, Ohmichi M, Inaba Y: [Sodium azide: a review of biological effects ad case reports] [Japanese]. Nippon Eiseigaku Zasshi 1999;53:572.
68. Senda T, Nishio K, Hori Y, et al: [A fatal case of fatal acute sodium azide poisoning] [Japanese]. Chudoku Kenkyu 2001;14:339.
69. Bennett MC, Mlady GW, Kwon Y-H, Rose GM: Chronic in vivo sodium azide infusion induces selective and stable inhibition of cytochrome c oxidase. J Neurochem 1996;66:2606.
70. Bennett CM, Mlady GW, Fleshner M, Rose GM: Synergy between chronic corticosterone and sodium azide treatments in producing a spatial learning deficit and inhibiting cytochrome oxidase activity. Proc Natl Acad Sci U S A 1996;93:1330.
71. Smith RP, Louis CA, Kruszyna R, Kruszyna H: Acute neurotoxicity of sodium azide and nitric oxide. Fundam Appl Toxicol 1991;17:120.
72. Judge KW, Ward NE: Fatal azide-induced cardiomyopathy presenting as acute myocardial infarction. Am J Cardiol 1989;64:830.
73. Klein-Schwartz W, Gorman RL, Oderda G, et al: Three fatal sodium azide poisonings. Med Toxicol Adverse Drug Exp 1989;4:219.
74. Vieira Lopes LC, Campello AP: Effect of hydroxocobalamin on the inhibition of cytochrome *c* oxidase by cyanide. I. In intact mitochondria. Res Comm Chem Pathol Pharmacol 1975;12:521.