Terrorism Involving Cyanide: The Prospect of Improving Preparedness in the Prehospital Setting

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Abbreviations:
CAK = Cyanide Antidote Kit
CDC = United States Centers for Disease Control and Prevention

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Abstract

The potential for domestic or international terrorism involving cyanide has not diminished and in fact may have increased in recent years. This paper discusses cyanide as a terrorist weapon and the current state of readiness for a cyanide attack in the United States. Many of the factors that render cyanide appealing to terrorists are difficult to modify sufficiently to decrease the probability of a cyanide attack. For example, the relative ease with which cyanide can be used as a weapon without special training, its versatile means of delivery to intended victims, and to a large degree, its ready availability cannot be significantly modified through preparedness efforts. On the other hand, the impact of an attack can be mitigated through preparedness measures designed to minimize the physical, psychological, and social consequences of cyanide exposure. Although the nation remains ill-equipped to manage a cyanide disaster, significant progress is being realized in some aspects of preparedness. Hydroxocobalamin—a cyanide antidote that may be appropriate for use in the prehospital setting for presumptive cases of cyanide poisoning—currently is under development for potential introduction in the US. If it becomes available in the US, hydroxocobalamin could enhance the role of the prehospital emergency responder in providing care to victims of a cyanide disaster. Additional progress is required in the areas of ensuring local and regional availability of antidotal treatment and supportive interventions, educating emergency healthcare providers about cyanide poisoning and its management, and raising public awareness of the potential for a cyanide attack and how to respond.

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Introduction

The increasingly salient public health threat of disasters involving cyanide and the lack of preparedness in the US for such events were described in 2001.[1] In the wake of the 11 September 2001 attacks on the World Trade Center and the Pentagon, the threat of a disaster caused by chemical, biological, or other substances that can be used as weapons of mass destruction has become only more palpable.

The fact that cyanide, in particular, continues to pose a public health threat is illustrated by several recent findings representative of a much larger number of incidents of intended or actual use of cyanide as a weapon.

1. *May 2002*: Ten tons of sodium cyanide were stolen during a truck hijacking in Mexico. Weeks later, only one fifth of the cyanide had been recovered, and the hijackers had not been found.
2. *June 2002*: Joseph Konopka (Dr. Chaos) was indicted by a US grand jury on counts of possessing the chemical weapons sodium cyanide and potassium cyanide, which he stored in the Chicago subway system.
3. *November 2003*: The US Department of Homeland Security issued a warning to law enforcement personnel about al-Qaeda's development of a device for producing cyanogen chloride and hydrogen cyanide gases for dispersal through ventilation systems.

Blood agents
• Hydrogen Cyanide
• Cyanogen Chloride
Nerve agents
• Tabun
• Sarin
• Soman
• VX
Vesicants
• Lewsite
• Nitrogen and sulfur mustards
Pulmonary agents
• Phosgene
• Chlorine

Table 1—Categories of chemical weapons[4–6]

4. *September 2004*: South Korea indicated that North Korea imported approximately 175 tons of sodium cyanide from South Korea through China and Thailand in 2003. This amount of cyanide is eclipsed by the nearly 3,800 tons of sodium cyanide exported from South Korea to Thailand from 2002 to the present. Exports such as these have been characterized as a security threat, as most of the countries that import sodium cyanide from Korea are not members of and do not consider themselves bound by the directives of the Australia Group. The Australia Group is a 38-member consortium that attempts to ensure that exported material does not contribute to the proliferation of biological and chemical weapons.

The potential for domestic or international terrorism involving cyanide has not diminished and in fact, it may have increased in recent years. In the context of this continued threat, has the ability of the healthcare system to manage a chemical terrorism attack involving cyanide changed? This paper discusses cyanide as a potential terrorist weapon and the current state of domestic readiness for a cyanide attack.

Profile of Cyanide as a Terrorist Weapon

The Centers for Disease Control and Prevention (CDC) and the Department of Homeland Security include cyanide, known among many in the military as a blood agent, among the most probable agents of chemical terrorism.[2,3] Other main categories of chemical weapons include nerve agents such as sarin and VX, blister agents such as nitrogen and sulfur mustards, and pulmonary agents such as phosgene and chlorine (Table 1).[4–6] The classification of cyanide as a blood agent originated from the perception that cyanide is carried in the blood and that its primary site of action is the bloodstream.[7] This classification is outdated, and somewhat misleading because the primary site of action of cyanide is not necessarily the bloodstream. Although cyanide is carried in the blood, so too are other chemical weapons including absorbed nerve agents. Therefore, the term does not differentiate cyanide from other categories of chemical weapons.

Cyanide has a long history of use as a murder weapon, terrorist weapon, and weapon of war as well as an agent of suicide and attempted genocide. The characteristics of cyanide are those of the ideal terrorist weapon:[2,4] (1) cyanide can cause mass physical and psychological casualties; (2) it is readily available; (3) it is versatile with respect to how it can be delivered; and (4) it does not require specialized skills or knowledge for effective use. Finally, effective management of moderate-to-severe cyanide poisoning requires specific resources (i.e., an antidote) that are available typically in short supply. Therefore, the chances of responding effectively to an attack generally are low.

Cyanide kills cells by preventing them from using oxygen, and necessitating anaerobic cellular metabolism, which generates cytotoxic byproducts.[8] The oxygen deprivation and accumulation of cytotoxins are thought to be the principal mechanisms of cyanide toxicity, although additional mechanisms also may contribute. Acute cyanide poisoning is manifested by symptoms including stupor, seizures, and coma, and can culminate in death within seconds to hours, depending on the concentration, source, and route of cyanide exposure.[9] The dramatic, alarming manifestations of poisoning and the deadliness of cyanide make it suitable for accomplishing the primary aim of terrorists of inciting mass fear and panic by incapacitating or killing large numbers of individuals.

The ready availability of cyanide also renders it an attractive terrorist weapon. Worldwide, an estimated 1.84 billion pounds of hydrogen cyanide are produced each year.[10] Cyanide is manufactured in large quantities in the US and other countries for use in industrial processes including electroplation, extraction of gold and silver from ores, fumigation, and the production of nitriles.[11] Cyanide also is available in research laboratories. Cyanide is susceptible to theft from these laboratories and industrial sources as well as from the railroads and trucks used in transport. The May 2002 robbery of 10 tons of cyanide during the truck hijacking in Mexico illustrates the ease of obtaining cyanide.

Available in both gaseous and solid forms, cyanide is versatile with respect to mode of delivery to intended victims. Hydrogen cyanide gas can be released into enclosed spaces such as stadiums, public transportation vehicles, and office buildings. Al-Qaeda's device for dispersing cyanide through ventilation systems presumably was developed for this application. In salt form, cyanide can be introduced into the water supply, food, and pharmaceuticals as exemplified by the plans of four Moroccans arrested in February 2002 in Rome to poison the US Embassy's water supply with cyanide; the more than 900 deaths caused by cyanide-laced Kool-Aid® in 1978 in Jonestown among Reverend Jim Jones' followers; and the frequent use of cyanide-laced pharmaceuticals as weapons in incidents including the

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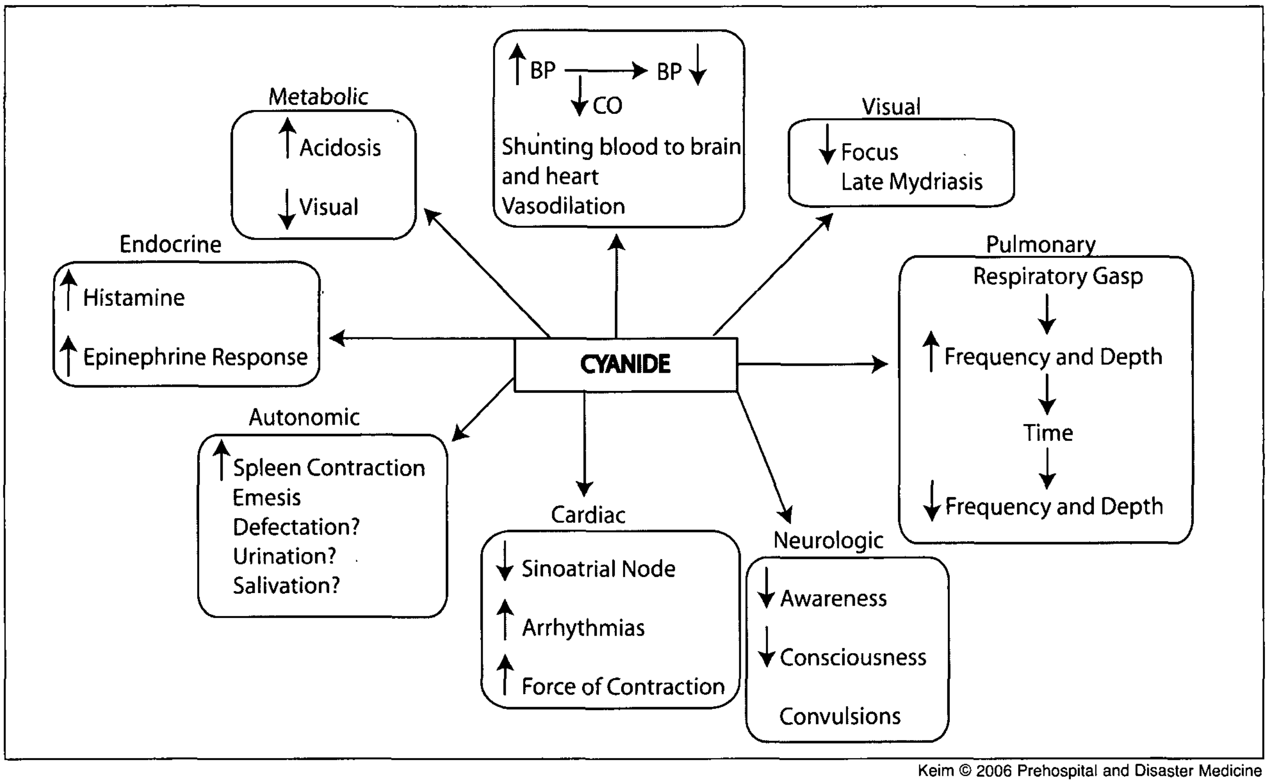

Figure 1—Cyanide causes progressive tissue hypoxia[9]

1982 Tylenol® murders of seven Chicagoans, the 1986 Excedrin® murders of two people in Washington, and the 2003 Vanilla Coke® murder of a Maryland teenager. While not planned necessarily by terrorists as a source of cyanide poisoning, smoke caused by a fire from an explosion or conflagration constitutes another potentially important source of cyanide in a terrorist attack.

As these examples of planned or actual use of cyanide as a weapon suggest, the use of cyanide as a weapon does not require specialized skills or knowledge. The lack of requirements for specialized training or expertise both increases the number of possible candidates who can successfully implement cyanide attacks, and helps contain the expense involved in planning and implementing these attacks.

Cyanide also is an attractive weapon for terrorists because of the lack of availability of effective means of managing acute cyanide toxicity, particularly when multiple victims are involved. Moderate-to-severe poisoning requires the prompt use of specific antidotes to prevent death. Given the rapid lethality of cyanide, effective management of a cyanide disaster involving multiple victims would require the rapid dissemination of large quantities of antidote and its nearly immediate administration. These requirements cannot be met in the current healthcare environment, in which many hospitals and emergency vehicles fail to stock the antidote or do not stock a sufficient number of antidote kits for a multiple-casualty disaster.[12–14] This point is illustrated by the results of a 21-hospital survey assessing preparedness for chemical terrorist attacks in a major US city between 1996 and 2000—a time during which the federal government markedly increased spending on bioterrorism preparedness with the passage of the 1996 Nunn-Lugar-Domenici Defense Against Weapons of Mass Destruction Act (WMD Act).[14] The results show that preparedness for a cyanide emergency was inadequate in both 1996 and 2000. In 1996, the number of cyanide antidote kits across the 21 hospitals was 276. In 2000, the number was 35. Moreover, in 1996, two of the 21 hospitals met the minimum preparedness criterion of at least 50 cyanide antidote kits in inventory. In 2000, none of the hospitals met this criterion.

The rapid administration of antidote as required in a terrorist incident also is hindered by the difficulty in diagnosing acute cyanide poisoning. Signs and symptoms of cyanide poisoning are general, nonspecific manifestations of oxygen deprivation (Figure 1), and none definitively indicate the presence of cyanide poisoning. Furthermore, no blood test or other diagnostic is available that can rapidly return results within the time required for effective intervention.[9] The inability to confirm a diagnosis of cyanide poisoning rapidly at the disaster scene necessitates treatment of the basis of a presumptive diagnosis if treatment is to be administered in time to be effective. Administration of antidote based on a presumptive diagnosis of cyanide poisoning is problematic because the Cyanide Antidote Package (also known as the Cyanide Antidote Kit (CAK), the Pasadena Kit, the Taylor Kit, and the Lilly Kit), the only cyanide antidote currently marketed in the US, can cause potentially life-threatening toxicities.[15–17] The risks of administering the CAK in the prehospital setting may outweigh the benefits in the event that a patient is treated for cyanide poisoning but does not in fact suffer from cyanide toxicity.

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-Appears to be effective in use in France
-Confirmatory studies for United States regulators
    -Animal efficacy
    -Healthy volunteer safety
-Does not reduce oxygen carrying capacity of blood
-Does not cause hemodynamic instability
-Transient side effects
    -Discoloration of urine, mucous membranes
    -(Clinically insignificant) abnormalities in colormetric laboratory tests

Risk:benefit ratio renders it suitable for prehospital empiric use

Figure 2—Characteristics of the cyanide antidote hydroxocobalamin

The CAK includes amyl nitrite administered via a mechanical ventilation device or by gauze sponge for inhalation as well as sodium nitrite and sodium thiosulfate, both of which are administered intravenously. The nitrite components of the kit form methemoglobin in the process of neutralizing cyanide. Nitrite-induced methemoglobinemia can be toxic because it reduces the ability of the blood to carry oxygen.[1] Methemoglobinemia is dangerous, especially for smoke-inhalation victims, who may have concurrent carboxyhemoglobinemia because of exposure to carbon monoxide. Besides causing methemoglobinemia, the CAK can cause severe hypotension, leading to shock.[17] Administration of the thiosulfate component alone is not a viable solution for these problems because sodium thiosulfate has a slow onset of antidotal action.[18] Therefore, it most often is used in conjunction with other rapidly acting agents rather than as a single antidote. Because of its safety liabilities, the CAK seldom is administered outside of the hospital. In the context of the need for presumptive diagnosis of acute cyanide poisoning, the potential harm associated with administration of the CAK renders the decision of whether or not to initiate antidotal therapy the most challenging one in an out-of-hospital triage situation potentially involving cyanide.[19]

Adequate Preparedness: An Attainable Goal

Many of the factors that render cyanide appealing to terrorists are difficult to modify to the extent required to decrease the probability of a cyanide attack. For example, the relative ease with which cyanide can be used as a weapon without special training, its versatile means of delivery to intended victims, and to a large degree its ready availability cannot be significantly modified through preparedness efforts. On the other hand, the impact of an attack can be mitigated through preparedness measures designed to minimize the physical, psychological, and social consequences of cyanide exposure.

Cyanide preparedness could also be enhanced dramatically in the US by introduction of a cyanide antidote that is effective, easily administered, and sufficiently safe to be given in the prehospital setting for presumptive cases of cyanide poisoning.[1] Such an antidote is currently marketed in France as Cyanokit® (hydroxocobalamin) (Figure 2). Hydroxocobalamin, a precursor of vitamin B_{12}, is present naturally in the body in small amounts.[20] Hydroxocobalamin detoxifies cyanide by binding with it to form cyanocobalamin, which is excreted in urine, without compromising the oxygen-carrying capacity of the blood or causing hypotension or other clinically relevant adverse events.[16,20,21] Data on the pharmacokinetics and the use of hydroxocobalamin in the prehospital setting are discussed elsewhere in this supplement.[8]

Hydroxocobalamin appears to have no major toxicities.[8] The most common side effects of hydroxocobalamin include the discoloration of urine and mucous membranes and abnormalities in specific colorimetric laboratory tests. These effects, which arise from the red color of the hydroxocobalamin molecule, are transient (lasting 1–3 days), and do not appear to reflect clinically meaningful changes. With this safety profile, hydroxocobalamin could be administered at disaster scenes so that intervention is not delayed until hospital care can be provided. Moreover, hydroxocobalamin need not be reserved for cases of confirmed cyanide poisoning, but could be administered in cases of suspected poisoning. Therefore, hydroxocobalamin could make more rapid initiation of treatment more feasible than with the CAK, and thereby, potentially improve outcomes in a cyanide disaster. The ability to use a cyanide antidote empirically at the disaster scene could significantly improve the readiness of the US to respond to terrorist attacks and other disasters involving cyanide.

Although hydroxocobalamin still is not available in the US, it currently is under development for potential introduction as an antidote. Additionally, new studies to further establish its antidotal profile are in progress. (Although hydroxocobalamin is currently approved in the US for the treatment of pernicious anemia, the 1 mg/mL concentration marketed for this use is too dilute for use as an antidote. In France, the hydroxocobalamin antidote is available in a 2.5 g vial.) The usual dose in France is 5 g (2 vials) administered intravenously.

Successful preparedness for a cyanide attack involves stockpiling sufficient quantities of antidote to respond in the event of an attack involving multiple victims. Should hydroxocobalamin be made available in the United States, stocking practices must be reassessed, and means of ensuring rapid distribution and adequate regional and local supply will need to be developed.

According to a 2000 task force comprising of members of the US CDC, law enforcement personnel, and intelligence defense agencies, stockpiling chemical antidotes is

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- Enhance epidemiologic capacity for detecting and responding to chemical attacks
- Enhance awareness of chemical terrorism among emergency medical service personnel, police officers, firefighters, physicians, and nurses
- Stockpile chemical antidotes
- Develop and provide bioassays for detection and diagnosis of chemical injuries
- Prepare educational materials to inform the public during and after a chemical attack

Table 2—Improving preparedness for chemical attacks[2]

one of five major activities that local, state, and federal public health organizations should implement to enhance preparedness for chemical attacks (Table 2).[2] For the US to be prepared for a chemical attack involving cyanide, public health organizations must develop action plans for and allocate resources to each of these five preparedness activities. Because enhancing preparedness for chemical attacks involves the same skills and resources that managing non-terrorism-related chemical accidents does, improving readiness for chemical terrorism should also improve the capability to recognize and respond to chemical injuries arising from causes other than terrorism.

Conclusions

Although the nation remains ill-equipped to manage a cyanide disaster, significant progress is being realized in some aspects of preparedness. Advances in antidote therapy may provide an intervention that can be administered in the prehospital setting for presumptive cases of cyanide poisoning. Additional progress is required in the areas of ensuring local and regional availability of antidotal treatment and supportive interventions, educating emergency health care providers about cyanide poisoning and its management, and raising public awareness of the potential for a cyanide attack and how to respond.

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