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Standard Form 298 (Rev. 8-98)
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Diagnosis and Treatment of Cyanide Toxicity

David J. Barillo, MD, FACS

The role of cyanide toxicity in victims of fire has been extensively examined in both the medical and the fire literature in the 1970s, 1980s, and 1990s. A large clinical series and comprehensive literature review was published in the burn literature in 1994. Since that time, several articles have revisited this issue, in part prompted by the availability of a new cyanide antidote kit. The combustion of certain household furnishings can produce cyanide. Cyanide can be detected in trace amounts in the smoke at house fires and in the blood of both smokers and fire victims. Ingestion of cyanide produces metabolic acidosis, an acid-base derangement also seen in burn patients during resuscitation. Proponents of the “cyanide poisoning” theory of smoke inhalation link these facts and draw the conclusion that fire victims need to be treated with cyanide antidotes. Such studies do not consider the fire environment, the inherent inaccuracies in cyanide assay, the fact that cyanide is a normal human metabolite, the capability of the body to detoxify cyanide, or the evidence that cyanide can be produced in vitro by normal human blood and in situ in certain organs after death.

Smoke, defined as “the airborne solid and liquid particulates and fire gases evolved when a material undergoes pyrolysis or combustion” contains over 400 toxic compounds, including carbon monoxide, polyvinyl chloride, carbon dioxide, aldehydes, acrolein, oxides of nitrogen, and cyanide. Cyanide is produced by the combustion of natural or synthetic household materials, including synthetic polymers, polyacrylonitrile, paper, polyurethane, melamine, wool, horsehair, and silk. It is presently not possible to predict the physiologic interactions of all toxins produced in smoke, and such prediction would be of little clinical utility as the number and ratio of toxins produced will vary minute-by-minute in a house fire. Fire is a complex and dynamic phenomena, and structure fires typically pass thru several phases, where the fuel-to-oxygen ratio, the type and amount of toxic substances produced, and the amount of heat generated are all different. During active burning, the oxygen concentration in a fire decreases to 10 to 15%, a point at which asphyxiation will occur. Hypoxia, elevated lactate levels, and metabolic acidosis, considered to be “hallmarks” of cyanide poisoning, are more likely a consequence of exposure to the oxygen deficient atmosphere of a typical house fire, carbon monoxide poisoning, or both.

Temperatures in a fire room can easily reach 1000 to 2100°F (537–1160°C). This is significant because smoke is not only toxic, but flammable, and many of the toxins in smoke will readily burn. Hydrogen cyanide has a flash point of 0°F (temperature at which a substance will give off sufficient flammable vapor for ignition to occur) and a NFPA 704 flammability index of 4 (equal to hydrogen). Ignition of cyanide without a flame source (auto-ignition) occurs at 1000°F (538°C). Although cyanide can be produced in fires, it is likely that cyanide is also rapidly consumed in fires. The best demonstration of this point is data collected from a burn test of a recreation of an actual fire disaster.

In 1981, a fire in the Stardust Nightclub in Dublin, Ireland resulted in 48 fatalities and 214 injuries. As part of the fire investigation, a model of the nightclub was reconstructed and intentionally burned as a scientific study. Davies reported on the prospectively studied toxins in the smoke produced by this test burn. Cyanide levels immediately after ignition measured approximately 250 parts per million (ppm), but decreased to approximately 10 ppm at 8 minutes postignition, and remained lower thereafter. In a related study, Burgess et al. measured cyanide levels in smoke during actual house fires using sampling devices placed on the turnout coats of Boston firefighters. Hydrogen cyanide was detected in 27 of 253 samples, with a 5-minute maximum concentration of 3.6 ppm. Neither the short-term exposure limit (15 ppm),
the immediate danger to life and health limit (50 ppm) nor the short-term lethal concentration (350 ppm) were exceeded. On this basis, the study concluded that cyanide posed little risk to firefighters.13

Should smoke inhalation victims be tested for cyanide exposure? Advocates note that diagnosis of cyanide poisoning in smoke inhalation victims is difficult, as the clinical symptoms mimic acute anxiety reactions38,39 or carbon monoxide exposure.28,40 Unfortunately, a simple and rapid blood assay for cyanide is lacking, and would be of questionable utility even if available as cyanide is an intracellular poison. When blood cyanide assay is performed for research or forensic purposes, the results are confusing. Cyanide is a normal metabolite30,41 in humans and can be both produced and degraded in blood samples in vitro. After death, cyanide can be produced by brain, liver, kidney, uterus, stomach, and intestinal tissue. Putrefaction of organs can yield cyanide levels of 10 mg/L or over three times the “fatal” level.23 Erythrocytes can convert thiocyanate to cyanide in vitro,42 and because blood cyanide is mainly bound to erythrocytes,42,43 autolysis of red blood cells may elevate blood cyanide levels. In normal individuals, blood cyanide levels range from up to 0.3 mg/L in nonsmokers to 0.5 mg/L in smokers.41,43–45 Firefighters, despite chronic smoke exposure, seem to have relatively normal blood cyanide levels.1 Cyanide is mildly elevated in both fire survivors and in fire fatalities. A significant or fatal blood cyanide level is usually defined as 3 mg/L,6,16,38,44,46–49 although levels as low as 1 mg/L14,15,50,51 or as high as 5 mg/L45 have been cited. Most proponents of the cyanide poisoning theory of smoke inhalation incorrectly use 1 mg/L as a marker of significant or fatal exposure. Measured cyanide levels in fire survivors average from 0.02 to 3.1 mg/L, with levels up to 6.5 mg/L reported.1 Survival with blood cyanide levels of 7 to 9 mg/L has been documented after cyanide ingestion52 or inhalation.23

Should smoke inhalation victims be treated for cyanide exposure? Recommendations for the treatment of cyanide poisoning in smoke victims are extrapolated from limited industrial experience or from suicide or homicide victims. Cyanide poisoning is not a common event and little human data is available.53 A 100-year literature review of cyanide poisoning found 61 reported cases, with magnitude of exposure (blood cyanide levels) documented in only four patients.47 Statistics collected by the American Association of Poison Control Centers revealed only 337 reported cyanide exposures over a 2-year period, with 22 patients experiencing major symptoms and eight patients expiring.44 More recently, 10-year data from the same organization has been published showing similar results with 3165 human exposures, 413 patients with moderate or severe symptoms and 80 deaths.6 The classic treatment approach by Chen and Rose54,55 is based on small-scale animal studies performed in 193454,56 and involves the oxidation of hemoglobin to methemoglobin, which preferentially binds cyanide, forming cyanomethemoglobin.45 As cyanomethemoglobin dissociates, free cyanide is converted to thiocyanate by liver mitochondrial enzymes (rhodanase), using colloidal sulfate or thiosulfate as a substrate.57 Thiocyanate is then excreted in the urine. This regimen forms the basis of the oft-mentioned “cyanide antidote kit” which includes amyl nitrite perles, 10% sodium nitrite, and 25% sodium thiosulfate. Despite the popularity of this kit, documentation of effectiveness is limited. One review found that “no quantitative tests for cyanide in blood or gastric aspirate were ever reported in either Chen’s or Rose’s cases, or in any other reports attesting to the combination antidotes (nitrite/thiosulfate) they advocate.”47 Intravenous sodium nitrite causes significant and sometimes fatal side effects, including severe hypotension, cardiovascular instability, instability under anesthesia, or worsening hypoxia.45,58,59,66 A methemoglobin level of 20 to 30% is required to optimally bind cyanide. Dimethylaminophenol is also sometimes used to induce methemoglobinemia in cyanide poisoning.

Sodium thiosulfate acts as a substrate in the conversion of cyanide to thiocyanate, and is proportioned to be an effective antidote when used with or without nitrite.45,61 Prospective clinical trials of the single agent use of thiosulfate for cyanide poisoning are lacking and human use is largely based on case studies.2 Sodium thiosulfate is felt to act more slowly than other cyanide antidotes. Administration at recommended doses carries no serious side effects63 although nausea, retching, and vomiting have been reported.

In Europe, cyanide poisoning is treated with cheating agents such as dicobalt edetate (Kelocyanor) or hydroxycobalamin (vitamin B12a). Kelocyanor has been associated with anaphylactic reactions and can produce severe hypertension, cardiac arrhythmias, or cobalt poisoning when given in the absence of cyanide.44,61 A combination of amyl nitrite and Kelocyanor is used in Great Britain.62 Kelocyanor is not available in the United States.

Hydroxycobalamin is an effective cyanide antidote employing a dose of 100 mg/kg. In the United States, hydroxycobalamin historically has been available in 1 mg/ml concentrations limiting its usefulness,63 as approximately 10 L would be needed to

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neutralize a fatal (200 mg) cyanide dose. Recent concerns over possible use of cyanide as a terrorist weapon have encouraged orphan drug approval (under the FDA Animal Efficacy Rule) of hydroxycobalamin in a 5-g dose for the indication of cyanide poisoning. In 2007, Dey Pharmaceuticals released a 5-g dose as the “cyanokit” with a wholesale cost of $800 a treatment. The smoke inhalation market is being aggressively targeted with claims of “ten years of experience in Europe.” In the author’s opinion, cyanide poisoning is both overdiagnosed and overtreated in Europe, where the 1 mg/L blood cyanide level is considered as significant or fatal. Kelocyanor and hydroxycobalamin are used together in France where a kit containing 4 g of hydroxycobalamin is available.

Hydroxycobalamin therapy has been used to prevent cyanide toxicity in patients receiving intravenous nitroprusside and to treat toxic amyllobia and optic neuritis caused by the cyanide present in tobacco smoke. Hydroxycobalamin therapy is usually well tolerated, but has been associated with side effects of headache, allergic reaction, skin and urine discoloration, hypertension, or reflex bradycardia. Hydroxycobalamin administration may also interfere with the accuracy of co-oximetry or autoanalyzer colorimetric blood assay for liver enzymes, electrolytes, and minerals, an effect which lasts for several days. Rare anaphylactic reactions have been reported.

Hyperbaric oxygen therapy for cyanide has been advocated by some, whereas others have demonstrated no benefit, and objective data remains to be collected. An elevated blood lactate, elevated base deficit or metabolic acidosis is often quoted as proof of cyanide poisoning in smoke or burn victims. In reality, under-resuscitation, coexisting traumatic injury, carbon monoxide poisoning, missed associated traumatic injury or a combination of the three and cyanide treatment should not be instituted until these conditions have been ruled out.

An elevated blood lactate, elevated base deficit or metabolic acidosis is often quoted as proof of cyanide poisoning in smoke or burn victims. In reality, under-resuscitation, coexisting traumatic injury, carbon monoxide poisoning, or exposure to an oxygen-deficient atmosphere are more likely causes. In either case, aggressive resuscitation and administration of 100% oxygen is indicated. Increased oxygen delivery may increase respiratory secretion of cyanide, reactivate mitochondrial enzymes, and activate other oxidative systems.

The need for specific antidotes in (fire or nonfire) cyanide poisoning is controversial. Aggressive supportive therapy aimed at the restoration of cardiovascular function augments the hepatic clearance of cyanide without specific antidotes and should be the first line of treatment. Survival of severe poisoning (blood levels of 5.6–9 mg/L) after cyanide ingestion or smoke inhalation has been documented when aggressive supportive therapy has been used without cyanide antidotes.

CONCLUSIONS

Although cyanide poisoning does not seem to play any significant role in human smoke inhalation injury, the science both affirming and refuting this fact is largely anecdotal, retrospective, or based on small-scale animal studies. In terms of future research needs, the first priority would be the development of a rapid cyanide assay to document actual cyanide poisoning before any antidote administration is considered. Ideally, this should be a noninvasive test similar to a breathalyzer or a pulse oximeter, to allow prehospital use. Because cyanide is an intracellular poison, development of a rapid assay will be difficult. Once an accurate and rapid cyanide assay is available, prospective studies can be designed to address the efficacy of antidote regimens. Because the expected incidence of true cyanide poisoning in smoke inhalation victims is very small, a large multicenter study will be required.

The recent availability of a new cyanide antidote kit, coupled with widespread marketing as a smoke inhalation “treatment” raises concerns for the burn community. Metabolic acidosis in a burn patient must be assumed to represent under-resuscitation, carbon monoxide poisoning, missed associated traumatic injury or a combination of the three and cyanide treatment should not be instituted until these conditions have been ruled out. Treatment of metabolic acidosis with hydroxocobalamin may delay appropriate consultation and/or transfer to a specialized burn treatment facility. Thus, the initial research priority for the burn community should be to document use, complications, and delay in consultation or transfer resulting from treatment of suspected cyanide “poisoning” in smoke inhalation injury.

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Effects of Toxic Gases: Methamphetamine Inhalation

Sandra M. Wells, PhD,* Curtis Noonan, PhD,* Kathryn M. Wells, MD,†
Andrij Holian, PhD,* Lucy A. Wibbenmeyer, MD‡

Methamphetamine (MA) is a substituted amphetamine with potent central nervous system stimulant effects. It is currently the most widespread illegally used stimulant and most prevalent synthetic drug manufactured in the US. It can be easily manufactured in clandestine laboratories using readily available materials including the precursor substances ephedrine, pseudoephedrine, and phenylpropanolamine. The manufacturing of MA presents serious dangers due to the volatile chemicals, toxic byproducts, and potential for fires and explosions that can result in injuries and burns. In addition to the precursor chemicals, over 30 different chemicals can be used to produce MA, many of which are highly reactive, corrosive, and ignitable substances. MA laboratories pose a danger to the individual producing the drug, anyone present during the production, the community surrounding the production site, and the law enforcement personnel who discover the laboratory.

Legislation and negotiation with source areas for precursor substances have reduced the availability of the raw materials needed to make the drug. On March 9, 2006, the Federal Combat Methamphetamine Epidemic Act of 2005 was enacted. This law requires drugs containing ephedrine, pseudoephedrine, and phenylpropanolamine to be kept behind pharmacy counters and purchased only after identification and sign-in of the buyer, as well as limit purchases to no more than 9 grams per 30-day period. The legislation also adds further restrictions on the impact of MA precursor chemicals through increased accountability to Federal regulators at the points of distribution and enhances penalties for persons manufacturing MA in areas where children reside. As a consequence, there has been a nationwide drop in