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Diagnosis and Treatment of Cyanide Toxicity

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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.[1] Since that time, several articles have revisited this issue,[2–12] 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[13] and in the blood of both smokers and fire victims.[14–18] 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.[2,3,19–22] 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.[23]

Smoke, defined as "the airborne solid and liquid particulates and fire gases evolved when a material undergoes pyrolysis or combustion"[24] 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,[15,25,26] polyacrylonitrile,[19,27] paper,[27] polyurethane,[19,26,28,29] melamine,[29] wool,[15,19,27] horsehair,[30] and silk.[15,19,27]

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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%,[31,32] a point at which asphyxiation will occur. Hypoxia, elevated lactic acid levels, and metabolic acidosis, considered to be "hallmarks" of cyanide poisoning,[3] 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).[33,34] 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)[35] and a NFPA 704 flammability index of 4 (equal to hydrogen).[36,37] Ignition of cyanide without a flame source (auto-ignition) occurs at 1000°F (538°C).[36] 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[33] 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[13] 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 reactions[38,39] 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 metabolite[30,41] 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/L[14,15,50,51] or as high as 5 mg/L[45] 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 ingestion[52] 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 Rose[54,55] is based on small-scale animal studies performed in 1934[54,56] and involves the oxidization 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.[45,58,59,60] 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 proported 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 effects[8,33] although nausea, retching, and vomiting have been reported.

In Europe, cyanide poisoning is treated with chelating 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

neutralize a fatal (200 mg) cyanide dose.[62] 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.[3] In 2007, Dey Pharmaceuticals released a 5-g dose as the "cyanokit" with a wholesale cost of $800 a treatment.[4] 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[44] where a kit containing 4 g of hydroxycobalamin is available.[63]

Hydroxycobalamin therapy has been used to prevent cyanide toxicity in patients receiving intravenous nitroprusside[59] and to treat toxic amblyopia and optic neuritises caused by the cyanide present in tobacco smoke.[64,65] Hydroxycobalamin therapy is usually well tolerated,[44,59] but has been associated with side effects of headache, allergic reaction, skin and urine discoloration, hypertension, or reflex bradycardia.[2,3,4,6] Hydroxycobalamin administration may also interfere with the accuracy of co-oximetry[4,10] or autoanalyzer colorimetric blood assay for liver enzymes, electrolytes, and minerals,[2,6] an effect which lasts for several days.[7] Rare anaphylactic reactions have been reported.[2]

Hyperbaric oxygen therapy for cyanide has been advocated by some,[20,44,61,66–69] whereas others have demonstrated no benefit,[70,71] and objective data remains to be collected.[72]

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, underresuscitation, 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.[3]

The need for specific antidotes in (fire or nonfire) cyanide poisoning is controversial.[1,4,44,7,73] Aggressive supportive therapy aimed at the restoration of cardiovascular function augments the hepatic clearance of cyanide without specific antidotes[31] and should be the first line of treatment. Survival of severe poisoning (blood levels of 5.6–9 mg/L) after cyanide ingestion[38,47,52,74] or smoke inhalation[15] 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.[4] 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.[1,56,75] 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.

REFERENCES

1. Barillo DJ, Goode R, Esch V. Cyanide poisoning in victims of fire: analysis of 364 cases and review of the literature. J Burn Care Rehabil 1994;15:46–57.
2. Hall AH, Dart R, Bogdan G. Sodium thiosulfate or hydroxocobalamin for the empiric treatment of cyanide poisoning? Ann Emerg Med 2007;49:806–13.
3. Borron SW. Recognition and treatment of acute cyanide poisoning. J Emerg Nurs 2006;32:S12–8.
4. Erdman AR. Is hydroxocobalamin safe and effective for smoke inhalation? Searching for guidance in the haze. Ann Emerg Med 2007;49:814–6.
5. Nelson L. Acute cyanide toxicity: mechanisms and manifestations. J Emerg Nurs 2006;32:S8–11.
6. DesLauriers CA, Burda AM, Whal M. Hydroxocobalamin as a cyanide antidote. Am J Ther 2006;13:161–5.
7. Borron SW, Baud FJ, Megarbane B, Chantal B. Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation. Am J Emerg Med 2007;25:551–8.
8. Houeto P, Hoffman JR, Imbert M, Levillain P, Baud FJ. Relation of blood cyanide to plasma cyanocobalamin concen-

tration after a fixed dose of hydroxocobalamin in cyanide poisoning. Lancet 1995;346:605–8.
9. Koschel MJ. Where there's smoke, there may be cyanide. Am J Nurs 2002;102:39–42.
10. Lee J, Mukai D, Kreuter K, Mahon S, Tromberg B, Brenner M. Potential interference by hydroxocobalamin on cooximetry hemoglobin measurements during cyanide and smoke inhalation treatments. Ann Emerg Med 2007;49:802–5.
11. Hantson P, Butera R, Clemessy JL, Michel A, Baud FJ. Early complications and value of initial clinical and paraclinical observations in victims of smoke inhalation without burns. Chest 1997;111:671–5.
12. Schnepp R. Cyanide: sources, perceptions and risks. J Emerg Nurs 2006;32:S3–6.
13. Burgess WA, Treitman RD, Gold A. Air contaminants in structural firefighting. Springfield, VA: National Technical Information Service Publication PB 299017, US Department of Commerce; 1979.
14. Silverman SH, Purdue GF, Hunt JL, Bost RO. Cyanide toxicity in burned patients. J Trauma 1988;28:171–6.
15. Clark CJ, Campbell D, Reid WH. Blood carboxyhaemoglobin and cyanide levels in fire survivors. Lancet 1981;1: 1332–5.
16. Wetherell HR. The occurrence of cyanide in the blood of fire victims. J Forensic Sci 1966;11:167–73.
17. Barillo DJ, Goode R, Rush BF, Lin RL, Freda A, Anderson EJ. Lack of correlation between carboxyhemoglobin and cyanide in smoke inhalation injury. Curr Surg 1986;43:421–3.
18. Barillo DJ, Rush BF, Goode R, Lin RL, Freda A, Anderson EJ. Is ethanol the unknown toxin in smoke inhalation injury? Am Surg 1986;52:641–5.
19. Prien T, Traber DL. Toxic smoke compounds and inhalation injury—a review. Burns 1988;14:451–60.
20. Hart GB, Strauss MB, Lennon PA, Whitcraft DD. Treatment of smoke inhalation by hyperbaric oxygen. J Emerg Med 1985;3:211–15.
21. Demling RH, LaLonde C. Burn trauma. New York: Theime Medical Publishers, Inc.; 1989. p. 5–7.
22. Federal Emergency Management Agency, United States Fire Administration. The medical management of victims of smoke and toxic gas inhalation. Washington DC: U.S. Government Printing Office (FA-79); 1988.
23. Curry AS, Price DE, Rutter ER. The production of cyanide in post mortem material. Acta Pharmacol Toxicol 1967;25: 339–44.
24. American Society of Testing & Materials. Standard terminology relating to fire standards [ASTM E176-82]. Philadelphia: American Society of Testing & Materials; 1982.
25. Woolley WD. Nitrogen containing products from the thermal decomposition of flexible polyurethane foams. Br Polym J 1972;4:27–43.
26. Bell RH, Stemmer KL, Barkley W, Hollingsworth LD. Cyanide toxicity from the thermal degradation of rigid polyurethane foam. Am Ind Hyg Assoc J 1979;40:757–62.
27. Terrill JB, Montgomery RR, Reinhardt CF. Toxic gases from fires. Science 1978;200:1343–7.
28. Cahalane M, Demling RH. Early respiratory abnormalities from smoke inhalation. JAMA 1984;251:771–3.
29. Fein A, Leff A, Hopewell PC. Pathophysiology and management of the complications resulting from fire and the inhaled products of combustion: review of the literature. Crit Care Med 1980;8:94–8.
30. Anderson RA, Harland WA. Fire deaths in the Glasgow area. III. The role of hydrogen cyanide. Med Sci Law 1982;22: 35–40.
31. Cohen MA, Guzzardi LJ. Inhalation of products of combustion. Ann Emerg Med 1983;12:628–32.
32. Demling RH. Physiologic changes in burn patients. In: Wilmore DW, Brennan MF, Harken AH, Holcroft JW, Meakins JL, editors. American College of Surgeons care of the surgical patient. New York: Scientific American, Inc.; 1991.
33. Davies JWL. Toxic chemicals versus lung tissue-an aspect of inhalation injury revisited. J Burn Care Rehabil 1986;7: 213–22.
34. National Fire Protection Association. Standard methods of fire tests of building construction and materials [NFPA 251]. Quincy, MA: National Fire Protection Association; 1990.
35. Henry MF, editor. Hazardous materials response handbook. Quincy, MA: National Fire Protection Association; 1989. p. 58–9.
36. National Fire Protection Association. Fire hazard properties of flammable liquids, gases and volatile solids [NFPA 325M]. Quincy, MA: National Fire Protection Association; 1991.
37. National Fire Protection Association. Identification of the fire hazards of materials [NFPA 704]. Quincy, MA: National Fire Protection Association; 1990.
38. Vogel SN, Sultan TR, Ten Eyck RP. Cyanide poisoning. Clin Toxicol 1981;18:367–83.
39. Koschel MJ. Management of the cyanide-poisoning patient. J Emerg Nurs 2006;32:S19–26.
40. Jones GRN. Cyanide and fire victims [Letter]. Lancet 1988; 2:457.
41. Symington IS, Anderson RA, Thomson I, Oliver JS, Harland WA, Kerr JW. Cyanide exposure in fires. Lancet 1978;2: 91–2.
42. Ballantyne B. In vitro production of cyanide in normal human blood and the influence of thiocyanate and storage temperature. Clin Toxicol 1977;11:173–93.
43. Ballantyne B. Artifacts in the definition of toxicity by cyanides and cyanogens. Fundam Appl Toxicol 1983;3:400–8.
44. Hall AH, Rumack BH. Clinical toxicology of cyanide. Ann Emerg Med 1986;15:1067–74.
45. Ivankovich AD, Braverman B, Kanuru RP, Heyman HJ, Paulissian R. Cyanide antidotes and methods of their administration in dogs: a comparative study. Anesthesiology 1980; 52:210–6.
46. Gettler AO, Baine JO. The toxicology of cyanide. Am J Med Sci 1938;195:182–98.
47. Graham DL, Laman D, Theodore J, Robin ED. Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. Arch Intern Med 1977;137:1051–5.
48. Jones J, McMullen MJ, Dougherty J. Toxic smoke inhalation: cyanide poisoning in fire victims. Am J Emerg Med 1987;5:317–21.
49. Hartzell GE. Combustion products and their effects on life safety. In: Cote AE, Linville JL, editors. Fire protection handbook. 17th ed. Quincy, MA: National Fire Protection Association; 1991:3.3–3.14.
50. Buchwald A. Cyanide toxicity [Letter]. Ann Emerg Med 1989;18:1257.
51. Becker CE. The role of cyanide in fires. Vet Hum Toxicol 1985;27:487–90.
52. Caravati EM, Litovitz TL. Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. JAMA 1988; 260:3470–2.
53. Berlin C. Cyanide poisoning—a challenge [Editorial]. Arch Intern Med 1977;137:993–4.
54. Chen KK, Rose CL, Clorves GHA. Comparative values of several antidotes in cyanide poisoning. Am J Med Sci 1934; 188:767–81.
55. Chen KK, Rose CL. Treatment of acute cyanide poisoning. JAMA 1956;162:1154–5.
56. Barillo DJ. Use of cyanide antidotes in smoke inhalation injury is potentially dangerous study says [Letter[. Fire Eng 1994;147:26.
57. Levine MS, Radford EP. Occupational exposures to cyanide in Baltimore fire fighters. J Occup Med 1978;20:53–6.
58. Hall AH, Kulig KW, Rumack BH. Suspected cyanide poisoning in smoke inhalation: complications of sodium nitrite therapy. J Toxicol Clin Exp 1989;9:3–9.
59. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf

H. Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 1978;298:809–11.
60. Garnier R, Bismuth C, Riboulet-Delmas G, Efthymiou ML. Poisoning from fumes from polystyrene fire. Br Med J (Clin Res Ed) 1981;283:1610–1.
61. Langford RM, Armstrong RF. Algorithm for managing injury from smoke inhalation. BMJ 1989;299:902–5.
62. Anonymous. Which antidote for cyanide? Lancet 1977;2: 1167.
63. Davies J. Challenges for the future. In: Haponik EF, Munster AM, editors. Respiratory injury: smoke inhalation and burns. New York: McGraw-Hill Co.; 1990. p. 389.
64. Pettigrew AR, Fell GS. Simplified colorimetric determination of thiocyanate in biological fluids, and its application to investigation of the toxic amblyopias. Clin Chem 1972;18: 996–1000.
65. Vincent M, Vincent F, Marka C, Faure J. Cyanide and its relationship to nervous suffering. Physiopathological aspects of intoxication. Clin Toxicol 1981;18:1519–27.
66. Workman WT, Calcote RD. Hyperbaric oxygen therapy and combat casualty care: a viable potential. Mil Med 1989;154: 111–5.
67. Takano T, Miyazaki Y, Nashimoto I, Kobayashi K. Effect of hyperbaric oxygen on cyanide intoxication: in situ changes in intracellular oxidation reduction. Undersea Biomed Res 1980;7:191–7.
68. Trapp WG. Massive cyanide poisoning with recovery: a boxing day story. Can Med Assoc J 1970;102:517.
69. Meyer GW, Hart GB, Strauss MB. Hyperbaric oxygen therapy for acute smoke inhalation injuries. Postgrad Med 1991; 89:221–3.
70. Litovitz TL, Larkin RF, Myers RA. Cyanide poisoning treated with hyperbaric oxygen. Am J Emerg Med 1983;1: 94–101.
71. Way JL, End E, Sheehy MH, et al. Effect of oxygen on cyanide intoxication. IV. Hyperbaric oxygen. Toxicol Appl Pharmacol 1972;22:415–21.
72. Grube BJ. Therapeutic hyperbaric oxygen: help or hindrance in burn patients with carbon monoxide poisoning? [Letter]. J Burn Care Rehabil 1989;10:285.
73. Cohen MA, Guzzardi L. A letter on the treatment of cyanide poisoning. Vet Hum Toxicol 1984;26:503–4.
74. Brivet F, Delfraissy JF, Duche M, Bertrand P, Dormont J. Acute cyanide poisoning: recovery with non-specific supportive therapy. Intensive Care Med 1983;9:33–5.
75. Roberts JR. Review of cyanide poisoning in victims of fire. In: Wagner DK, eds. 1995 Yearbook of Emergency Medicine. Mosby, Inc; 26.

Effects of Toxic Gases: Methamphetamine Inhalation

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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.[1] 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.[2] 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.[3] On March 9, 2006, the Federal Combat Methamphetamine Epidemic Act of 2005 was enacted.[4] 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

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