Carbon monoxide poisoning

Michael C. Dolan,* MD

Carbon monoxide poisoning is a significant cause of illness and death. Its protean symptoms probably lead to a gross underestimation of its true incidence. Low levels of carbon monoxide aggravate chronic cardiopulmonary problems, and high levels are associated with cardiac arrhythmias and cerebral edema. Patients who survive acute poisoning are at risk of delayed neurologic sequelae. The measurement of carboxyhemoglobin levels does not reveal the tissue levels of carbon monoxide but is useful in determining therapy. Treatment includes the monitoring and management of cardiac arrhythmias and oxygenation. Hyperbaric oxygenation is beneficial, but there are currently no definite criteria for its use.

L'intoxication par le monoxyde de carbone rend compte d'une morbidité et d'une mortalité importantes. Mais la variabilité de sa symptomatologie en fait sans doute sous-estimer la fréquence. L'intoxication même légère aggrave les troubles cardio-pulmonaires préexistants; plus importante, elle détermine des arythmies cardiaques et l'oedème cérébral. Les sujets qui survivent à une intoxication aiguë sont exposés à des séquelles neurologiques à retardement. La carboxyhémoglobinémie, si elle ne renseigne pas sur la concentration tissulaire du monoxyde de carbone, sert quand même de guide pour la thérapeutique. Outre l'oxygénation, celle-ci comporte le dépistage et le traitement des arythmies. Si l'oxygénothérapie hyperbare est utile, ses indications sont encore à préciser.

Carbon monoxide poisoning is the leading cause of death from poisoning in the United States,[1] accounting for approximately 3500 accidental or suicidal deaths per year.[2] The incidence of nonlethal poisoning is very difficult to assess; one early report suggested a 2:1 survival ratio,[3] but this is probably a gross underestimation, as the protean symptoms of nonlethal poisoning often lead to misdiagnosis.[4-6] The most common misdiagnosis is flu-like viral illness;[6,7] other misdiagnoses range from pseudotumour cerebri[5] to acute myocardial infarction.[6] Grace and Platt[6] ranked carbon monoxide poisoning with syphilis, tuberculosis and subdural hematoma in its ability to mimic a variety of systemic diseases. The incidence of carbon monoxide poisoning is likely to increase as fuel costs rise, more people use wood fuels, and housing is made more airtight.[8,9]

*Clinical fellow, Department of Emergency Medicine, University of Louisville, Louisville, Kentucky

Reprint requests to: Dr. Michael C. Dolan, Department of Emergency Medicine, University of Louisville, School of Medicine, Louisville, KY 40292, USA

Sources

Catabolism of hemoglobin and other heme-containing compounds to bilirubin and carbon monoxide accounts for a baseline carboxyhemoglobin (COHb) level of less than 1%. This level increases in patients with hemolytic anemias.[10] Methylene chloride, a constituent of many paint strippers, is converted in vivo to carbon monoxide. This source is particularly hazardous since the COHb level continues to increase after cessation of exposure; when the level begins to decrease it does so slowly.[11]

The major source of carbon monoxide is the incomplete combustion of organic fuels. Internal-combustion engine exhaust may contain up to 8% carbon monoxide and still meet US emission standards,[12] although there is evidence that the implementation of emission standards has reduced the carbon monoxide production of newer vehicles.[13] Vehicle exhaust is particularly hazardous in enclosed spaces, such as garages or the holds of ships.[14] The use of gas-powered ice-surfacing machines has led to carbon monoxide poisoning in skating rinks.[15-18] Johnson and colleagues[15] have described 15 such cases; these children were initially thought to have food poisoning, another common misdiagnosis.[19]

Fires are an obvious source of carbon monoxide, with smoke containing 0.1% to 10% carbon monoxide[20] and several other potentially toxic gases.[21,22] In a 2-year study of fire-related deaths in New York Zikria and associates[23] found that 58.9% of the victims who had survived less than 12 hours after injury had had carbon monoxide poisoning and that 24.3% had had lethal levels of COHb. Inadequate venting of furnaces, water heaters and space heaters can cause lethal levels of carbon monoxide,[6,7,24] as can charcoal fires in enclosed spaces.[25] Incomplete combustion of canned fuels used to heat food (e.g., Sterno) can also produce toxic amounts of carbon monoxide.[26] Air pollution can be associated with a baseline COHb level of up to 2% in nonsmokers.[27]

Cigarette smoking is a significant source of carbon monoxide, producing COHb levels of 5% to 9%.[27,28] "Sidestream" smoke, which is emitted by the burning tip of a cigarette, contains two and a

half times more carbon monoxide than "mainstream", inhaled smoke.[29] Cigarette smoking in night clubs and taverns can produce hazardous levels of carbon monoxide when the ventilation is inadequate.[30] Nonsmokers exposed to sidestream smoke (so-called "passive smokers") absorb carbon monoxide.[31]

Pathophysiologic features

Carbon monoxide is taken up by the lungs, the uptake being proportional to the minute volume. Metabolism to carbon dioxide has a minor effect on carbon monoxide stores, the main route of excretion being via the lungs. Excretion is also dependent on the minute volume.[32]

Carbon monoxide combines with hemoglobin, depending on the partial pressures of carbon monoxide and oxygen;[33] however, carbon monoxide's affinity for hemoglobin is 230 to 260 times that of oxygen.[34] With this high affinity, rapid breathing during heavy exercise can cause a 30% rise in the COHb level after 2 minutes' exposure to 1% carbon monoxide.[20] A level of 0.4% can be fatal after 1 hour.[35]

Peterson and Stewart[36] exposed human volunteers to various concentrations of carbon monoxide for 30 minutes to 24 hours. Blood COHb levels were determined during exposure and up to 23 hours after exposure. Treatment was carried out with oxygen at one and three atmospheres of pressure. The investigators measured the half-life of COHb in room air at an average of 320 (extremes, 128 and 409) minutes. They felt that the variations in half-life could be attributed to differences between the subjects and their activity levels. At normal pressure 100% oxygen reduced the half-life of COHb to an average of 80.3 minutes; at three atmospheres of pressure it further decreased the half-life to an average of 23.3 minutes.

COHb shifts the oxyhemoglobin dissociation curve to the left, so the oxygen that is still bound to hemoglobin is not as readily available at the cellular level, which results in a lower tissue oxygen pressure than that seen with similar levels of simple hypoxia.[37] Many authors believe that the toxic effect of carbon monoxide is due to hypoxia alone,[25,26,38,39] but there is evidence that binding to heme-containing proteins at the cellular level also has a role.

Ten to fifteen percent of the total body carbon monoxide is located in the extravascular tissues.[40] This percentage increases at COHb levels greater than 55% and with hypoxia.[10,32] Carbon monoxide competes with oxygen for cytochrome a_3, but oxygen's affinity is nine times greater under normal conditions.[41] In the transition from anoxia to normoxia as little as 0.01% carbon monoxide can profoundly impair the cytochrome chain.[42] Carbon monoxide has been observed to have direct toxic effects on mammalian lung tissue through inhibition of the cytochrome chain.[43] Electron microscopic studies of neural and cardiac tissue in rats have demonstrated a greater decrease in cytochrome oxidase activity with carbon monoxide poisoning than with a comparable level of hypoxia.[44] Carbon monoxide binds to cardiac and skeletal muscle myoglobin, with cardiac muscle taking up about three times as much as skeletal muscle.[40] During hypoxemia, carboxymyoglobin loads increase significantly.[40] Carboxymyoglobin dissociation is slower than COHb dissociation, accounting for a rebound of COHb to significant levels several hours after therapy has resulted in low levels.[45] The ratio of cardiac carboxymyoglobin to circulating COHb is approximately 3:1,[40] which indicates that in individuals with a COHb level of 10%, approximately 30% of cardiac myoglobin is saturated with carbon monoxide. This significantly decreases the oxygen reserve available to the myocardium.

Clinical manifestations

The effects of carbon monoxide poisoning are apparent in most body systems but are most pronounced in areas of high blood flow and oxygen demand (i.e., the heart and brain). The initial symptoms are nonspecific. Of 184 victims of acute carbon monoxide poisoning 90% had headache, 82% dizziness, 53% weakness, 46% nausea, 46% trouble in thinking, 40% shortness of breath, 26% visual problems and 6% loss of consciousness.[24] Headache, dizziness, weakness and trouble in thinking correlated well with duration of exposure. Increased temperature is not uncommon, nor is mild hypertension.[14] Diarrhea can also occur.[19] In view of these symptoms it is not surprising that flu-like illness is the most common misdiagnosis, particularly when further questioning reveals that a roommate or family member is having similar symptoms. If carbon monoxide poisoning is not considered in patients with these symptoms they may return to a hazardous environment, with disastrous results.[5,6] Carbon monoxide poisoning resulting from the use of inadequately vented heating devices tends to occur with the onset of cold weather, coincident with the "flu season".

Cherry-red skin discoloration, so long thought to be typical of carbon monoxide poisoning, is uncommon.[46] Skin vesicles commonly develop at pressure points in comatose patients.[47,48] Bullous lesions may also develop in areas not subject to pressure, and sweat-gland necrosis has been reported.[48] Rhabdomyolysis can occur either secondary to pressure necrosis in comatose patients[49,50] or as a direct cellular toxic effect in patients with long-term exposure.[50] Such patients are at risk of renal failure from myoglobinuria.[51]

There is an increase in the number of patients with pulmonary problems presenting to emergency departments during periods of high ambient carbon monoxide levels.[52] Patients with chronic obstructive lung disease have significantly reduced

exercise tolerance with a COHb level of 9%,[53] a level easily reached with heavy smoking. Low levels of carbon monoxide may have deleterious effects on cell structure in terminal airways.[43,54] A decrease in mid- and end-expiratory flow rates in nonsmokers who are chronically exposed to tobacco smoke has been attributed to carbon monoxide.[55] Acute carbon monoxide poisoning is associated with noncardiogenic pulmonary edema in up to 30% of cases.[56,57]

With low levels of COHb for long periods, cardiac performance, particularly in patients with coronary artery disease, is affected. Healthy coronary vessels will dilate in the presence of COHb and thus permit sufficient blood flow for adequate cellular oxygenation.[58] This compensatory mechanism is not present in patients with atherosclerosis, and low levels of COHb decrease the time to onset and increase the duration of angina pectoris.[59] Freeway travel in Los Angeles has been known to increase COHb levels to a mean of 4.96% and hence cause earlier onset of exercise-induced angina in patients with coronary atherosclerosis.[60] Ischemic ST-segment depression has been reported to occur in 3 of 10 patients who were breathing freeway air.[60] Passive smoking also aggravates angina pectoris.[61] Intermittent claudication occurs earlier than expected in patients with low levels of COHb,[62] and carbon monoxide poisoning has been implicated in the pathogenesis of atherosclerosis.[63,64] Long-term exposure to low levels of carbon monoxide causes polycythemia; however, the increase in the hemoglobin level is not an effective compensatory mechanism, since the level of intraerythrocytic 2,3-diphosphoglycerate decreases, and this results in impaired oxygen transport capability.[65,66]

The major cause of death associated with acute carbon monoxide poisoning is cardiac arrhythmia.[67] Premature ventricular complexes are common,[67] and infarcts can occur.[68] In patients with acute myocardial infarction the threshold for ventricular fibrillation is reduced in the presence of COHb levels as low as 9%.[69] There is an increased rate of death from myocardial infarction in high-pollution areas during periods of increased ambient carbon monoxide levels.[70] Patients who survive acute exposure are at risk of disability or death from the effects of carbon monoxide on the central nervous system.

Carbon monoxide poisoning may result in lethal cerebral edema as a consequence of cell death that is caused by hypoxia and interference with cellular respiration. Symmetric, destructive frontal and posterior parietal leukoencephalopathy occurs,[71] as do degenerative changes in the basal ganglia, especially the globus pallidus. Early computerized tomographic evidence of low-density areas in the globus pallidus in comatose patients correlates well with a high risk of death[72] or poor eventual outcome, as measured by the Glasgow Outcome Scale.[73]

Carbon monoxide poisoning is associated with visual field defects, paracentral scotomas, homonymous hemianopias, and temporary or permanent blindness. Papilledema may be seen on funduscopic examination.[74] Kelley and Sophocleus[5] found flame-shaped superficial retinal hemorrhages to be a sensitive indicator of subacute exposure to carbon monoxide and stressed the importance of funduscopic examination in patients with flu-like symptoms. Vestibular dysfunction and hearing loss have also been reported.[75]

Central nervous system disorders due to delayed neuropsychiatric or neurologic deterioration have long been recognized as a sequela of carbon monoxide poisoning. Delayed deterioration is also associated with diffuse demyelinization.[76] A 3-year follow-up of patients with carbon monoxide poisoning revealed that 11% suffered neuropsychiatric disturbances,[77] the most common being "affective incontinence", which included increased irritability, impulsiveness, mood changes, violence and verbal aggressiveness. Personality changes, cognitive abnormalities and neurologic abnormalities were common in patients with a decreased level of consciousness at the time of admission to hospital.

A review of 2360 victims of acute carbon monoxide poisoning revealed delayed neurologic sequelae in 3%; 98% of these had mental deterioration, 88% urinary or fecal incontinence, or both, and 81% gait disturbances.[78] Mutism, tremor, weakness and speech disturbances were also noted. Epilepsy is yet another consequence.[26] The onset of delayed symptoms may occur from 3 days to 3 weeks after exposure.[79]

Diagnosis

The diagnosis of carbon monoxide poisoning may be obvious if one is presented with a comatose patient who was found in a car with its motor running and a hose extending from the exhaust pipe to the driver's window. It is much less obvious when a husband and wife and their 18-month-old son present with nausea of abrupt onset, vomiting, diarrhea, abdominal cramps and headache.[19] The symptoms are so protean that carbon monoxide poisoning must be considered in the differential diagnosis of any flu-like syndrome. Since the presence of flame-shaped retinal hemorrhages is a sensitive but nonspecific indicator of subacute exposure to carbon monoxide, funduscopic examination should be performed routinely on patients with flu-like symptoms.[5] Patients with vague or flu-like symptoms should be asked questions about their possible exposure to sources of carbon monoxide, especially during cold months.

Determination of COHb levels is, at present, the best laboratory method for assessing exposure to carbon monoxide, since symptoms tend to correlate well with COHb levels (Table I). Some patients, however, may be asymptomatic and have high levels of COHb, as in one patient who had a COHb level of 58% but neither acute symptoms nor neurologic sequelae.[80] Conversely, treatment

with oxygen before a COHb sample is taken may produce a low level of COHb in patients who have severe symptoms.[81]

Myers and coworkers[81] advocated treatment for carbon monoxide poisoning in any unconscious patient who has a history compatible with poisoning, regardless of his or her COHb levels. They described four comatose patients who had circumstantial evidence of carbon monoxide poisoning but low or nonexistent levels of COHb; all four recovered completely with appropriate therapy. COHb levels do not indicate tissue levels of carbon monoxide.[40]

Arterial blood gas determinations do not reveal a low partial pressure of oxygen, as only the amount of oxygen physically dissolved in the blood is measured. The pH may be altered, reflecting lactic acidosis secondary to anaerobic metabolism.[82] Some authors have attempted to correlate the degree of acidosis with the prognosis,[83] but others have not found this useful.[84]

Psychometric testing has been used in an attempt to determine which patients require hyperbaric oxygen therapy. It involves six tests that attempt to assess comprehension, memory, spatial orientation, motor speed, fine motor control and visual coordination.[85] Preliminary reports indicate that psychometric testing may prove to be an accurate predictor of neurologic or neuropsychiatric sequelae.[86]

Treatment of acute exposure

As with exposure to any toxic agent, the victim must be removed from the source. Rescuers must take precautions if heavy exertion is required to remove the patient from an environment containing high levels of carbon monoxide. The mainstream of therapy is oxygen, and supplemental oxygen should be administered as soon as possible. Blood should be taken for measurement of the COHb level coincident with starting intravenous therapy.[87] Endotracheal intubation will be required for comatose patients. Low levels of continuous positive airway pressure should be used if there is evidence of inhalation injury.[88] The highest concentration of oxygen available should be administered. For patients not requiring intubation the use of a nonrebreathing mask and an oxygen flow of 10 L/min is recommended. A tight-fitting aviator-type mask is better but is usually not readily available. One hundred percent oxygen can supply one third of the body's oxygen demand by simple dissolution in plasma.[2] This therapy also shortens the half-life of COHb to 80.3 minutes.[36]

Cardiac rhythm should be monitored during transport and in the emergency department. Ventricular arrhythmias can be treated with lidocaine.[67] Electrocardiography should be done in the emergency department and blood samples sent for a complete blood count and determination of baseline levels of COHb, serum electrolytes, urea and creatinine, and arterial blood gases. Chest roentgenography and urinalysis should also be performed. If there has been prolonged stasis or if myalgia is a prominent complaint the serum creatine phosphokinase level should be measured and the urine checked for myoglobin.

It is essential to admit to hospital all patients with a COHb level greater than 25%, those with a history of cardiac decompensation and a COHb level of 15% or greater, and those with acidosis, electrocardiographic evidence of ischemia, impaired mentation and neurologic symptoms.[1,89] Patients not fitting into these categories should receive high-flow oxygen until their symptoms disappear and the COHb level is less than 10%. Patients admitted to hospital should receive cardiac monitoring and 100% oxygen. The optimum duration of administration of 100% oxygen has not been established. In Anderson's study,[45] patients with severe carbon monoxide poisoning received treatment until COHb was no longer detectable; however, several hours later its level increased significantly owing to tissue binding of carbon monoxide with slow release. This suggests that prolonged administration of oxygen and serial measurements of COHb levels would be prudent.

Table I—Symptoms commonly associated with various levels of carboxyhemoglobin (COHb)

Level of COHb (%)	Symptoms
0–10	None in healthy individuals Reduced exercise tolerance in patients with chronic obstructive pulmonary disease Decreased threshold for angina and claudication in patients with atherosclerosis
10–20	Headache, dyspnea on vigorous exertion
20–30	Throbbing headache, dyspnea on moderate exertion, difficulty with concentration, weakness
30–40	Severe headache, dizziness, nausea, vomiting, trouble in thinking, visual disturbances
40–50	Confusion, syncope on exertion
50–60	Collapse, convulsions
60–70	Coma, frequently fatal
> 70	Coma, death likely

Hyperbaric oxygen

The administration of 100% oxygen at three atmospheres of pressure causes sufficient oxygen to be dissolved in the blood for normal cerebral aerobic metabolism[45] and decreases the half-life of COHb to about 23 minutes.[36] Hyperbaric oxygen may also protect against cerebral anoxia,[90] cerebral edema[91] and demyelinization.[92] However, there is some controversy as to which patients should receive hyperbaric oxygen.[1,79,93] The development of psychometric testing may help to resolve this

controversy,[85,86] as may the study that is under way at the Porter Regional Baromedicine Center in Denver.[93] The administration of hyperbaric oxygen is a time-honoured therapy[94] and should be used for unconscious patients, those with neurologic symptoms caused by carbon monoxide poisoning and those in whom poisoning is suspected.[81] There is some evidence that patients treated with 100% normobaric oxygen can have a recurrence of symptoms 7 to 10 days after therapy.[85] These changes may be reversed with late hyperbaric oxygen therapy.[85] The duration of treatment with 100% normobaric oxygen in that study was not noted.

Hyperbaric oxygen is not readily available. At present there are no guidelines for the transfer of patients with carbon monoxide poisoning to facilities that use hyperbaric oxygen therapy; moreover, some concern has been expressed about transferring unstable patients when no controlled study has demonstrated superior results with hyperbaric oxygenation.[1] Early death is usually secondary to cardiac arrhythmias,[67] which are associated with levels of COHb as low as 9%.[69] Comatose patients with elevated COHb levels should therefore remain at the original hospital, receiving 100% oxygen and cardiac monitoring until the COHb level is less than 9%. Only if they remain comatose or have neurologic symptoms should they be transported to a distant centre; 100% oxygen should still be given during transportation. Comatose patients who are brought to hospital with low levels of COHb or none at all and strong circumstantial evidence of carbon monoxide poisoning could be transferred, while receiving 100% oxygen, after initial assessment and stabilization. This approach could be modified if a physician accompanied the patient during transfer.

Other

Various other treatments have been proposed for carbon monoxide poisoning, including hypothermia,[95,96] total body asanguineous hypothermic perfusion,[97] and exchange transfusion with whole blood[98] or perfluorochemical emulsion.[99] However, none of these have any clinical application at this time.

Conclusion

Acute carbon monoxide poisoning is the leading cause of death from poisoning in the United States. Practitioners must be aware of its presentation, diagnosis and therapy. They must also know the effects of low levels of carbon monoxide on the cardiovascular and respiratory systems so they can question patients who have experienced changes in angina patterns, those with increasing or earlier onset of claudication and those with earlier onset of dyspnea on exertion about their possible exposure to carbon monoxide. These patients and those with chronic obstructive lung disease must be made aware that the low levels of carbon monoxide in cigarette smoke can adversely affect their performance; smoking should thus be strongly discouraged. In addition, they should not allow themselves to passively inhale tobacco smoke in their home or work environment.

Subacute carbon monoxide poisoning is commonly misdiagnosed, so its actual incidence is not known. Since flu-like illness is the most common misdiagnosis, carbon monoxide poisoning must be included in the differential diagnosis of this common syndrome. It is perfectly acceptable after appropriate history-taking and physical examination to send a patient with headache, nausea, vomiting, weakness and a mild increase in temperature home, with the admonition to rest, drink plenty of liquids and call back in the morning. If, however, a patient has not been questioned about possible carbon monoxide exposure and returns to his house with its newly installed, inadequately ventilated furnace the result could be disastrous.

References

1. Olson KR: Carbon monoxide poisoning: mechanisms, presentation, and controversies in management. *J Emerg Med* 1984; 1: 233–243
2. Winter PM, Miller JN: Carbon monoxide poisoning. *JAMA* 1976; 236: 1502–1504
3. Shillito FH, Drinker CK, Shaughnessy TJ: The problem of nervous and mental sequelae in carbon monoxide poisoning. *JAMA* 1936; 106: 669–674
4. McBay AJ: Carbon monoxide poisoning. *N Engl J Med* 1965; 272: 252–253
5. Kelley JS, Sophocleus GJ: Retinal hemorrhages in subacute carbon monoxide poisoning. *JAMA* 1978; 239: 1515–1517
6. Grace TW, Platt FW: Subacute carbon monoxide poisoning. Another great imitator. *JAMA* 1981; 246: 1698–1700
7. Buckley AR: Still forgotten [C]. *Lancet* 1984; 1: 165–166
8. Carbon monoxide, an old enemy forgot [E]. *Lancet* 1981; 2: 75–76
9. Chalmers T: Tight houses, fresh air. *Fine Homebuild* 1984; 23: 4
10. Coburn RF: Endogenous carbon monoxide production. *N Engl J Med* 1970; 282: 207–209
11. Stewart RD, Hake CL: Paint remover hazard. *JAMA* 1976; 235: 398–401
12. Environmental Protection Agency: 40CFR 85 et seq, Washington
13. Hays P, Bornstein RA: Failed suicide attempt by emission gas poisoning. *Am J Psychiatry* 1984; 141: 592–593
14. Whorton MD: Carbon monoxide intoxication: a review of 14 patients. *JACEP* 1976; 5: 505–509
15. Johnson EJ, Moran JC, Paine SC et al: Abatement of toxic levels of carbon monoxide in Seattle ice-skating rinks. *Am J Public Health* 1975; 65: 1087–1090
16. Luckhurst DG, French W: Carbon monoxide in indoor skating arenas [C]. *Can Med Assoc J* 1979; 121: 1053–1054
17. Russell HL, Worth JA, Leuchak WP et al: Carbon monoxide intoxication associated with use of a gasoline powered resurfacing machine at an ice-skating rink — Pennsylvania. *MMWR* 1984; 33: 49–51
18. Kwok PW: Evaluation and control of carbon monoxide exposure in indoor skating arenas. *Can J Public Health* 1983; 74: 261–265
19. Castle SP, Lapham SC, Troutman WG et al: Carbon monoxide intoxication: diagnostic considerations [C]. *JAMA* 1984; 251: 2350
20. Stewart RD, Stewart RS, Stamm W et al: Rapid estimation of carboxyhemoglobin level in fire fighters. *JAMA* 1976; 235: 390–392

21. Clark CJ, Campbell D, Reid WH: Blood carboxyhemoglobin and cyanide levels in fire survivors. *Lancet* 1981; 1: 1332–1335
22. Cohen MA, Guzzardi LJ: Inhalation of products of combustion. *Ann Emerg Med* 1983; 12: 628–632
23. Zikria BA, Weston GC, Chodoff M et al: Smoke and carbon monoxide in fire victims. *J Trauma* 1972; 12: 641–645
24. Burney RE, Wu SC, Nemiroff MJ: Mass carbon monoxide poisoning: clinical effects and results of treatment in 184 victims. *Ann Emerg Med* 1982; 11: 394–399
25. Wilson EF, Rich TH, Messman HC: The hazardous hibachi. Carbon monoxide poisoning following use of charcoal. *JAMA* 1972; 221: 405–406
26. Murray TJ: Carbon monoxide poisoning from Sterno. *Can Med Assoc J* 1978; 118: 800–802
27. Stewart RD, Baretta ED, Plate LR et al: Carboxyhemoglobin levels in American blood donors. *JAMA* 1974; 229: 1187–1195
28. Russell MAH: Blood carboxyhemoglobin changes during tobacco smoking. *Postgrad Med J* 1973; 49: 684–687
29. Collishaw NE, Kirkbridge J, Wigle DT: Tobacco smoke in the workplace: an occupational health hazard. *Can Med Assoc J* 1984; 131: 1199–1204
30. Chappell SB, Parker RJ: Smoking and carbon monoxide levels in enclosed public places in New Brunswick. *Can J Public Health* 1977; 68: 159–161
31. Russell MAH: Absorption by non-smokers of carbon monoxide from room air polluted by tobacco smoke. *Lancet* 1973; 1: 576–579
32. Luomanmaki K, Coburn RF: Effects of metabolism and distribution of carbon monoxide on blood and body stores. *Am J Physiol* 1969; 27: 354–363
33. Douglas CG, Haldane JS, Haldane JBS: The laws of combination of haemoglobin with carbon monoxide and oxygen. *J Physiol [Lond]* 1912; 44: 275–304
34. Joels N, Pugh LG: The carbon monoxide dissociation curve of human blood. *J Physiol [Lond]* 1958; 142: 63–77
35. Finck PA: Exposure to carbon monoxide: review of the literature and 567 autopsies. *Milit Med* 1966; 131: 1513–1539
36. Peterson JE, Stewart RD: Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ Health* 1970; 21: 165–171
37. Roughton FJW, Darling RC: The effect of carbon monoxide on the oxyhemoglobin dissociation curve. *Am J Physiol* 1940; 141: 17–31
38. Murray TJ: Carbon monoxide in the modern society. *Can Med Assoc J* 1978; 118: 758–760
39. Jackson DL, Menges H: Accidental carbon monoxide poisoning. *JAMA* 1980; 243: 772–774
40. Coburn RF: The carbon monoxide body stores. *Ann NY Acad Sci* 1970; 174: 11–22
41. Ball EG, Strittmatter CF, Cooper O: The reaction of cytochrome oxidase with carbon monoxide. Ibid: 635–647
42. Chance B, Erecinska M, Wagner M: Mitochondrial responses to carbon monoxide toxicity. *Ann NY Acad Sci* 1970; 174: 193–204
43. Rhodes ML: The effect of carbon monoxide on mitochondrial enzymes in pulmonary tissue. *Am Rev Respir Dis* 1971; 103: 906
44. Somogyi E, Balogh I, Rubányi G et al: New findings concerning the pathogenesis of acute carbon monoxide (CO) poisoning. *Am J Forensic Med Pathol* 1981; 2: 31–39
45. Anderson GK: Treatment of carbon monoxide poisoning with hyperbaric oxygen. *Milit Med* 1978; 143: 538–541
46. Smith JS, Brandon S: Acute carbon monoxide poisoning — 3 years' experience in a defined population. *Postgrad Med J* 1970; 46: 65–70
47. Jones CTA, Mackay HAF: Carbon monoxide poisoning in a former mining community. *Br Med J* 1983; 286: 603–604
48. Leavell OW, Farley CH, McIntyre JS: Cutaneous changes in a patient with carbon monoxide poisoning. *Arch Dermatol* 1969; 39: 429–433
49. Orizaga M, Ducharme FA, Campbell JS et al: Muscle infarction and Volkmann's contracture following carbon monoxide poisoning. *J Bone Joint Surg [Am]* 1967; 49: 965–970
50. Finley J, VanBeek A, Glover JL: Myonecrosis complicating carbon monoxide poisoning. *J Trauma* 1977; 17: 536–540
51. Bessoudo R, Gray J: Carbon monoxide poisoning and nonoliguric renal failure. *Can Med Assoc J* 1978; 119: 41–44
52. Kurt TL, Mogielnicki RP, Chandler JE: Association of the frequency of acute cardiorespiratory complaints with ambient levels of carbon monoxide. *Chest* 1978; 74: 10–14
53. Caverley PMA, Leggett RJE, Flenley DC: Carbon monoxide and exercise tolerance in chronic bronchitis and emphysema. *Br Med J* 1981; 283: 878–880
54. Niden AH: The effects of low levels of carbon monoxide on the fine structure of the terminal airways. *Am Rev Respir Dis* 1971; 103: 898
55. White JR, Froeb HF: Small-airways dysfunction in nonsmokers chronically exposed to tobacco smoke. *N Engl J Med* 1980; 302: 720–723
56. Fein A, Grossman RF, Jones JG et al: Carbon monoxide effect on alveolar epithelial permeability. *Chest* 1980; 78: 726–731
57. Sone S, Higashihara T, Kotake T et al: Pulmonary manifestations in acute carbon monoxide poisoning. *Am J Roentgenol* 1974; 120: 865–871
58. Ayres SM, Giannelli S, Mueller H: Myocardial and systemic responses to carboxyhemoglobin. *Ann NY Acad Sci* 1970; 174: 268–293
59. Anderson EW, Andelman RJ, Strauch JM et al: Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. *Ann Intern Med* 1973; 79: 46–50
60. Aronow WS, Harris CN, Isbell MW et al: Effect of freeway travel on angina pectoris. *Ann Intern Med* 1972; 77: 669–676
61. Aronow WS: Effect of passive smoking on angina pectoris. *N Engl J Med* 1978; 299: 21–24
62. Aronow WS, Stemmer EA, Isbell MW: Effect of carbon monoxide exposure on intermittent claudication. *Circulation* 1974; 49: 415–417
63. Astrup P: Carbon monoxide, smoking and atherosclerosis. *Postgrad Med J* 1973; 49: 697–706
64. Sojka SG, Provan JL: Cigarette smoking and peripheral vascular disease: Is carbon monoxide the real culprit? *Can Med Assoc J* 1981; 125: 10–11
65. Astrup P: Intraerythrocytic 2,3-diphosphoglycerate and carbon monoxide exposure. *Ann NY Acad Sci* 1970; 174: 252–253
66. Thomas MF, Penney DG: Hematologic responses to carbon monoxide and altitude: a comparative study. *J Appl Physiol* 1977; 43: 365–369
67. Ginsberg MD, Myers RE: Experimental carbon monoxide encephalopathy in the primate: physiologic and metabolic aspects. *Arch Neurol* 1974; 30: 202–208
68. Anderson RF, Allensworth DC, DeGroot WJ: Myocardial toxicity from carbon monoxide poisoning. *Ann Intern Med* 1967; 67: 1172–1182
69. Debias DA, Banerjee CM, Birkhead NC: Effects of carbon monoxide inhalation on ventricular fibrillation. *Arch Environ Health* 1976; 31: 38–42
70. Cohen SI, Deane M, Goldsmith JR: Carbon monoxide and survival from myocardial infarction. *Arch Environ Health* 1969; 19: 510–517
71. Ginsberg MD, Myers RE, McDonagh BF: Experimental carbon monoxide encephalopathy in the primate. Clinical aspects, neuropathology and physiologic correlation. *Arch Neurol* 1974; 30: 209–216
72. Sawada Y, Sakameto T, Nishide K et al: Correlation of pathological findings with computed tomographic findings after acute carbon monoxide poisoning [C]. *N Engl J Med* 1983; 308: 1296
73. Sawada Y, Takahashi M, Ohashi N et al: Computerized tomography as an indication of long-term outcome after acute carbon monoxide poisoning. *Lancet* 1980; 1: 783–784
74. Dempsey LC, O'Donnell JJ, Hoff JT: Carbon monoxide retinopathy. *Am J Ophthalmol* 1976; 82: 692–693
75. Baker SR, Lilly DJ: Hearing loss from acute carbon monox-

ide intoxication. *Ann Otolaryngol* 1977; 86: 323–328
76. Plum F, Posner JB, Hain RF: Delayed neurological deterioration after anoxia. *Arch Intern Med* 1962; 110: 56–63
77. Smith JS, Brandon S: Morbidity from acute carbon monoxide poisoning at three-year follow-up. *Br Med J* 1973; 1: 318–321
78. Choi IS: Delayed neurologic sequelae in carbon monoxide intoxication. *Ann Neurol* 1983; 40: 433–435
79. Myers RAM: Carbon monoxide poisoning. *J Emerg Med* 1984; 1: 245–248
80. Davis S, Levy R: High carboxyhemoglobin level without acute or chronic findings. Ibid: 539–542
81. Myers RAM, Snyder SK, Linberg S et al: Value of hyperbaric oxygen in suspected carbon monoxide poisoning. *JAMA* 1981; 246: 2478–2480
82. Buehler JH, Berns AS, Webster JR et al: Lactic acidosis from carboxyhemoglobinemia after smoke inhalation. *Ann Intern Med* 1974; 82: 803–805
83. Larkin JM, Brahos GJ, Moylan JA: Treatment of carbon monoxide poisoning: prognostic factors. *J Trauma* 1976; 16: 111–114
84. Strohl KP, Feldman NT, Saunders NA et al: Carbon monoxide poisoning in fire victims: a reappraisal of prognosis. *J Trauma* 1980; 20: 78–80
85. Myers RAM, Mitchell JT, Cowley RA: Psychometric testing and carbon monoxide poisoning. *Disaster Med* 1983; 1: 279–281
86. Myers RAM, Messier LD, Jones DW et al: New directions in the research and treatment of carbon monoxide exposure. *Am J Emerg Med* 1983; 2: 226–230
87. Saxena K: Carbon monoxide poisoning situation encounters. *Disaster Med* 1983; 1: 277–278
88. Mathru M, Venus B, Rao TLK et al: Noncardiac pulmonary edema precipitated by tracheal intubation in patients with inhalation injury. *Crit Care Med* 1983; 11: 804–806
89. Myers RAM, Linberg SE, Cowley RA: Carbon monoxide poisoning: the injury and its treatment. *JACEP* 1979; 8: 479–484
90. Whalen RE, Heyman A, Saltzman H: The protective effect of hyperbaric oxygenation in cerebral anoxia. *Arch Neurol* 1966; 14: 15–20
91. Sukoff MH, Hollin SA, Jacobson JH: The protective effect of hyperbaric oxygenation in experimentally produced cerebral edema and compression. *Surgery* 1967; 62: 40–46
92. Fischer BH, Morton M, Reich T: Hyperbaric-oxygen treatment of multiple sclerosis. *N Engl J Med* 1983; 308: 181–186
93. Huber JA: Do awake patients with high carboxyhemoglobin levels need hyperbaric oxygen? *J Emerg Med* 1984; 1: 555–556
94. Norman JN, MacIntyre J, Shearer JR et al: Use of a one-man, mobile pressure chamber in the treatment of carbon monoxide poisoning. *Br Med J* 1970; 2: 333–334
95. Pierce EC II, Zacharias A, Alday JM Jr et al: Carbon monoxide poisoning: experimental hypothermic and hyperbaric studies. *Surgery* 1972; 72: 229–237
96. Boutros AR, Hoyt JL: Management of carbon monoxide poisoning in the absence of hyperbaric oxygenation chamber. *Crit Care Med* 1976; 4: 144–147
97. Agostini JC, Ramirez RG, Albert SN et al: Successful reversal of lethal carbon monoxide intoxication by total body asanguineous hypothermic perfusion. *Surgery* 1974; 75: 213–219
98. Yee LM, Brandon GK: Successful reversal of presumed carbon monoxide-induced semicoma. *Aviat Space Environ Med* 1983; 54: 641–643
99. Yokoyama K: Effect of perfluorochemical emulsion on acute carbon monoxide poisoning in rats. *Jpn J Surg* 1978; 8: 342–352

Incidence Less than 1%

1) Granulocytopenia (incidence about 0.5%), sometimes resulting in death
2) Thrombocytopenia
3) Immune hemolytic anemia
4) Convulsions
5) Psychosis with hallucinations
6) Confusion
7) Mental depression
8) Giddiness
9) Lightheadedness
10) Weakness
11) Bitter taste

Rare

1) Hypotension
2) A case was reported with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following a single dose of the drug.
3) Vasculitis (hypersensitivity-type).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and symptoms of overdosage of procainamide include severe hypotension, ventricular fibrillation, widening of the QRS complex, junctional tachycardia, intraventricular conduction delay, oliguria, lethargy, confusion, nausea and vomiting.

If ingestion is recent, gastric lavage or emesis may reduce absorption. Dopamine, phenylephrine or levarterenol may be helpful in reversing severe hypotensive responses.

Management of overdosage includes symptomatic treatment with ECG and blood pressure monitoring. Procainamide toxicity can usually be treated, if necessary, by administering vasopressors after adequate fluid volume replacement. Intravenous infusion of ⅙ molar sodium lactate injection reportedly reduces the cardiotoxic effects of procainamide.

The urinary elimination of procainamide is proportional to the glomerular filtration rate but is also affected by changes in urinary pH. Procainamide is relatively lipid-soluble as a free base but the ionized form is not. Acid urine, therefore, leads to ion trapping of procainamide which enters the urine by passive diffusion from the plasma. Accordingly, renal clearance of procainamide can be considerably increased by maintaining a low urinary pH and high flow rates.

If procainamide toxicity causes severe hypotension and renal insufficiency, urinary elimination of procainamide and NAPA is decreased and hemodialysis may be required. Hemodialysis significantly reduces the serum half-life of procainamide and effectively removes procainamide and NAPA. Peritoneal dialysis is not effective.

It has been reported that one patient who ingested approximately 7 g of procainamide hydrochloride recovered after treatment consisting of i.v. levarterenol, i.v. furosemide, attempted volume expansion with albumin, and hemodialysis. Also reported is the case of an elderly patient who recovered after ingestion of approximately 19 g of procainamide hydrochloride. The patient was treated with i.v. isoproterenol and i.v. epinephrine. The latter report suggested that insertion of a ventricular pacing electrode is a reasonable precautionary measure in case high grade SV block develops.

DOSAGE AND ADMINISTRATION

Selection of the dose and route of administration should be made with the following facts in mind:

1) The optimum plasma level is 4 to 8 mcg/mL.
2) In elderly patients and in patients with impaired renal function (decreased creatinine clearance) excretion is delayed and reduced frequency of administration is required (see PRECAUTIONS).
3) An alkaline urine indicates a reduction in excretion rate, and the necessity for reduced frequency of administration.
4) Patients with cardiac failure, shock, low cardiac output and extrarenal azotemia should be carefully monitored and the dose or frequency of administration reduced if necessary.
5) Excretion rates appear to be unchanged by furosemide and other diuretics but are decreased by the use of acetazolamide, due to the production of alkaline urine.
6) Should toxic or sub-therapeutic levels be suspected, the patient's plasma procainamide should be determined and adjusted accordingly.

Patients vary in response to a dose of procainamide. Nevertheless, the following **guidelines** should be considered when deciding upon the patient's actual requirements.

PRONESTYL-SR Tablets (procainamide hydrochloride tablets) are a sustained release dosage form not intended for initial therapy. For initial therapy by oral administration, conventional oral formulations of PRONESTYL (procainamide hydrochloride) are recommended. Patients stabilized to an appropriate dosage level can be transferred to an equivalent daily dosage regimen of PRONESTYL-SR tablets. The duration of action of procainamide hydrochloride supplied in this sustained release form allows dosing at intervals of every 6 hours, which may encourage patient compliance.

Ventricular Tachycardia and Premature Ventricular Contractions — The suggested maintenance dosage of PRONESTYL-SR Sustained Release Tablets is 50 mg/kg of body weight daily given in divided doses at six hour intervals.

To provide approximately 50 mg per kg per day:*

Give patients weighing less than 55 kg — 500 mg q6h

Give patients weighing between 55 and 91 kg — 500 mg or 1 g q6h

Give patients over 91 kg — 1 g q6h

*This dosage schedule is for use as a guide for treating the average patient; however, each patient must be considered on an individual basis.

Atrial Fibrillation and Paroxysmal Atrial Tachycardia — The suggested maintenance dosage of PRONESTYL-SR Sustained Release Tablets is 0.5 to 1 g every six hours.

Administration:

Patients should be advised not to break or chew the sustained-release tablet, as this would interfere with designed dissolution characteristics.

AVAILABILITY

Each greenish-yellow, biconvex, oval, veneer-coated sustained release tablet contains 500 mg of procainamide hydrochloride. Available in bottles of 100 and 500 tablets.

Storage: Store at room temperature; avoid excessive heat.

Product monograph available on request.