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Carbon Monoxide Poisoning

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Abstract

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I. INTRODUCTION

Carbon monoxide (CO) is a colorless, odorless, toxic gas that is a product of incomplete combustion. Motor vehicles, heaters, appliances that use carbon based fuels, and household fires are the main sources of this poison. Carbon monoxide (CO) intoxication is the leading cause of death due to poisoning in the United States.[1,2,3,4,5]. CO poisoning is also the most common cause of death in combustion related inhalation injury.[6,7] The incidence of non-lethal CO poisoning is not well established nor is that of unrecognized CO poisoning (subacute poisoning due to an unrecognized toxic CO exposure in the home or other indoor environment).[8]

II. EPIDEMIOLOGY

CO poisoning has been recognized for many centuries, soon after our ancestors attempted to build fires in non-ventilated shelters. The first accurate description of CO poisoning was recorded by Claude Bernard in 1857. Since then many advances in our understanding of the pathophysiology have been achieved.

The true incidence of CO poisoning is not known, since many non-lethal exposures go undetected.7 It has been estimated that one-third of all cases of CO poisoning are undiagnosed. This year 10,000 persons will seek medical attention or will miss at least one day of normal activity due to CO poisoning.[9] Mortality rates as high as 31% have been reported in large series, though in other surveys it has been only 1-2%.7 Nevertheless, from 1979 through 1988, unintentional deaths from CO poisoning in the United States have declined consistently.1

The most common sources for CO are listed below. CO from motor-vehicle exhausts is the single most common cause of poisoning deaths in the United.[10] Of the 11 547 unintentional CO deaths during 1979-1988, 57% were caused by motor vehicle exhausts; of these 83% were associated with stationary vehicles.10 Most motor-vehicle-related CO deaths in garages have occurred even though the garage doors or windows have been open, suggesting that passive ventilation may not be adequate to reduce risk in semi-closed spaces. Smoke inhalation from all types of fires is the second leading cause of CO poisoning. Most immediate deaths from building fires are due to CO poisoning and therefore, fire fighters are at high risk.

Exogenous Sources of CO

Epidemics of CO poisoning commonly occur during winter months and sources include misuse of non-electric heating or cooking devices as well as snow-obstructed motor vehicle exhaust systems. These epidemics are particularly common during winter storms due to power outages with the use of alternative methods of heating and cooking. [11,12]

It is well known that urban environments contain higher ambient CO concentrations, primarily due to automotive emissions, and non-smoking city dwellers have been found to have carboxyhemoglobin (COHb) levels in the 1-2% range.[13] Tobacco smoke is also a significant source of CO, containing approximately 4% CO; smokers have been observed to have COHb levels typically in the 4-5% range and as high as 9%. Hence, their COHb levels must be interpreted accordingly.

Methylene chloride (MC) deserves a special mention because it is contained in many paint removers and its

vapors are readily absorbed through the lungs. Once it reaches the circulation, MC is converted into CO in the liver.[14]

III. PATHOPHYSIOLOGY

In patients who die early following CO poisoning the brain is edematous, and there are diffuse petechia and hemorrhages. If the victim survives initially but dies within a few weeks, findings typical of ischemic anoxia are prominent. The pathologic findings is human victims have been reproduced in experimental animals poisoned with CO. Interestingly, the severity of the lesions appears to correlate best with the degree of hypotension rather than with hypoxia per se. [15]

I. HYPOXIA AND CELLULAR ASPHYXIA

CO combines preferentially with hemoglobin to produce COHb, displacing oxygen and reducing systemic arterial oxygen (O2) content. CO binds reversibly to hemoglobin with an affinity 200- 230 times that of oxygen.[16] Consequently, relatively minute concentrations of the gas in the environment can result in toxic concentrations in human blood. Possible mechanisms of toxicity include:

The most clear-cut mechanism by which CO toxicity occurs is competitive binding to the hemoglobin heme groups. This effect is magnified by the allosteric properties of the hemoglobin molecule. Its tetrameric structure undergoes a conformational change when CO is bound at one of the four heme sites, with a resulting increase in the affinity of the remaining heme groups for oxygen. This not only shifts the oxygen-hemoglobin dissociation curve to the left, but distorts its sigmoidal shape towards a hyperbola. The net result is a hemoglobin molecule that is poorly equipped to release oxygen at the tissue level. The decreased oxygen delivery is then sensed centrally, stimulating ventilatory efforts and increasing minute ventilation. The latter will increase uptake of CO and raise COHb levels, and will result in a respiratory alkalosis, further shifting the oxygen-hemoglobin dissociation curve to the left.

The mean half-life of COHb is 320 minutes (128-409) in young healthy volunteers on room air. Administration of one hundred percent O2 at one atmosphere reduces the half life to 80.3 minutes, while 100% O2 at three atmospheres will reduce the half life to 23.3 minutes.[17] CO binds to cardiac and skeletal myoglobin as well as hemoglobin (Hb). Cardiac myoglobin binds three times more CO than skeletal myoglobin.[18] Carboxymyoglobin dissociation is slower than COHb due to the increased affinity of CO for myoglobin. A "rebound effect" with delayed return of symptoms has occasionally been observed, corresponding to a recurrence of COHb elevation.[19] Presumably, this is due to late release of CO from myoglobin with subsequent binding to Hb.

While binding to the cytochrome P450 (mixed function oxidase) hemoprotein is known to occur, there have as yet been no demonstrable pathophysiologic consequences of this. Fetal hemoglobin binds CO more avidly than hemoglobin A, and with slow transplacental transport, fetal levels decrease much more slowly than in the mother. This accounts for the occurrence of occasional fetal death in nonfatal maternal exposures.[20]

II. ISCHEMIA.

In addition to causing tissue hypoxia, CO can cause injury by impairing tissue perfusion. Animal models of CO intoxication, as well as human experience, indicate that myocardial depression, peripheral vasodilation, and ventricular arrhythmia causing hypotension may be important in the genesis of neurologic injury. In animal models CO poisoning has been found to result in progressive hypotension, primarily as a result of peripheral vasodilation.[21]

III. REPERFUSION INJURY

Many of the pathophysiologic changes seen in CO poisoning are similar to those seen with postischemic reperfusion injuries, and similar pathology occurs in the brain in the absence of CO when hypoxic hypoxia precedes an interval of ischemia. [22] The generation of oxygen radicles during reperfusion has been implicated as the major component of postischemic brain injury.[23] Thom has reported that CO causes brain lipid peroxidation after, but not during CO exposure. [24] Furthermore, this investigator has demonstrated that pretreating rats with allopurinol prevents lipid peroxidation following CO exposure. [25] It is postulated that this oxidative injury is mediated largely by leukocytes. Leukocyte sequestration increases significantly in brain microvasculature following exposure to CO.[26] In rats made leukopenic or treated with monoclonal anti-CD-18 F(ab) fragments formation of xanthine oxidase and lipid peroxidation is inhibited following CO poisoning.26

IV. SYMPTOMATOLOGY

Many victims of CO poisoning die or suffer permanent, severe neurological injury despite treatment. In addition, as many as 50% of those who recover consciousness and

survive may experience varying degree of more subtle but still disabling neuropsychiatric sequela.[27]

The features of acute CO poisoning are more dramatic than those resulting from chronic exposure. At low COHb levels, chronic cardiopulmonary problems, such as angina and chronic obstructive pulmonary disease, may be exacerbated, since cardiac myoglobin binds with great affinity and rapidly reduces myocardial O2 reserve. Chest pain due to myocardial ischemia may occur, as can cardiac arrhythmias. Subacute or chronic CO poisoning presents with less severe symptoms and patients will initially be misdiagnosed as having other illnesses.8

The clinical presentation of acute CO poisoning is variable, but in general, the severity of observed symptoms correlates roughly with the observed level of COHb (Table 1); however, in terms of diagnostic value, the nonspecificity of these presenting symptoms makes definitive diagnosis difficult. There are several reports of levels near zero with patients showing neurologic deficits ranging from partial paralysis to coma. [28,29,30] Most of the data (Table 2) comes from experiments in healthy males, without the confounder of time lapse in specimen collection. With levels less than 10 percent the patient is usually asymptomatic. As COHb increases above 20 percent, the patient may develop headache, dizziness, confusion and nausea. Coma and seizures due to cerebral edema are common with levels greater than 40 percent, and death is likely above 60 percent.[31,32,33,34,35] In reality, pre-hospital delays and early oxygen therapy often with concomitant poisoning from cyanide make these symptom-level guidelines unreliable. Furthermore, the carboxyhemoglobin level per se has not been identified as a risk factor for CO-mediated morbidity or mortality. 4,33,[36,37,38]

The occurrence of illness in household pets concurrent with or just preceding the onset of a patients's own illness should alert to the possibility of CO poisoning.[39] Due to their smaller size and in general higher metabolic rates, pets may be more obviously and more severely affected by CO intoxication than their owners.

An array of neuropsychiatric problems have been reported to arise insidiously in some patients after their recovery from the acute effects of CO poisoning.4 Almost every type and degree of neurologic deficit has been described following recovery for acute CO poisoning. Up to 10% of survivors show gross neurologic or psychiatric impairment that is obvious to the physician, such as parkinsonism, persistent vegetative state, akinetic mutism, agnosia, apraxia, visual impairment, amnestic/confabulatory state or psychosis. 4,7,[40] Much more startling is the number of survivors who may develop persistent, albeit subtle, neuropsychiatric deficits. In a 3-year follow-up of 63 CO poisoning survivors, Smith and Brandon found that 33% showed evidence of personality deterioration and 43% reported memory impairment. 40

Table 1. COHb Levels and Symptomatology (Back to text)

V. DIAGNOSIS

A history of potential CO exposure is the most reliable indicator of poisoning. All patients at a fire scene should be evaluated for CO poisoning. Confirming the diagnosis may be difficult in some patients, as COHb may be low or undetectable because of the time between exposure and emergency department presentation.4

In evaluating a patient for CO poisoning several factors need to be considered. The patient needs to be examined for evidence of thermal injury or the presence of other gas inhalation. Elevated blood cyanide levels has been reported in victims of residential fires.[41] In this study a significant correlation was found between the HbCO and the blood cyanide concentration. Similarly, if the patient presents with CO poisoning as the result of a suicidal attempt, a drug screen as well as acetaminophen, salicylates and ethanol levels should be obtained.

An EKG should be obtained in all patients with or without symptoms, and if abnormal (commonly sinus tachycardia and ST-changes), serial creatine kinase (CK) and lactate dehydrogenase (LDH) determinations should be performed, and the patient kept under close observation.

It has been recommended that all CO poisoning patients undergo psychometric testing.7 However, short psychometric tests do not appear to correlate with the development of neuropsychiatric sequelae. It is also unclear whether treatment with HBO based on abnormal findings from these tests alone improve outcome. Furthermore, the current recommended tests have not been well validates in patients with CO poisoning and do not take into account learning from repeat administration. In patients with neuropsychiatric sequelae, a head CT or MRI scan may reveal characteristic abnormalities which include: bilateral necrosis of the globus pallidus as well as the cerebral cortex, hippocampus, and substantia nigra.4,7

VI. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of CO poisoning in the absence of a reliable history of exposure includes viral illnesses, food poisoning, depression, transient ischemic attack, coronary artery disease, arrhythmias and functional illnesses among others. The most common misdiagnosis is a "flu-like" syndrome.32 A recent report describes a 12 member family that presented to the emergency department in groups of 4 persons with symptoms consistent with food poisoning after drinking unrefrigerated milk.6 However, several other affected members of the same household had not consumed the same milk. Further investigation revealed severe CO poisoning which was found to be related to indoor barbecue grill usage that day.

VII. MANAGEMENT

The mainstay of therapy for CO poisoning is supplemental O2, ventilatory support and monitoring for cardiac arrhythmias. There is general agreement that 100% oxygen should be administered prior to laboratory confirmation when CO poisoning is suspected. The goal of oxygen therapy is to improve the O2 content of the blood by maximizing the fraction dissolved in plasma (PaO2).36 Once treatment begins, O2 therapy and observation must continue long enough to prevent delayed sequelae as carboxymyoglobin unloads. Unfortunately, there are no useful guidelines as to the length of the observation period.

The treatment of severe CO poisoning using additional modalities has been under investigation for several decades.7 Hypothermia, was used in the 1950s and 1960s in the management of these patients. However, at the beginning of the 1970s controlled studies showed no benefit in improving survival after severe CO poisoning.[42]

The most controversial and widely debated topic regarding CO poisoning is the use of hyperbaric oxygen (HBO).[43,44,45] Treatment utilizing HBO was first successfully used in Glasgow in the 1960's.[46] Since 1960, the clinical use of HBO for CO poisoning has occurred with increasing frequency. Over 2500 CO-intoxicated patients were treated in North American chambers in 1992. [47]

The rationale for the use of this HBO is based on the following information:

There is, however, little scientific evidence to support the benefit of HBO and no agreement on the selection of patients that may benefit from HBO treatment. Case reports, small case series and retrospective studies have suggested that mortality and morbidity among patients treated with HBO appears improved beyond that expected with ambient pressure supplemental oxygen therapy. 28,37,38 Thom and colleagues conducted a prospective, randomized, study in 60 patients with mild to moderate CO poisoning who presented within 6 hours. None of these patients had a history of loss of consciousness. Delayed neurological sequela developed in 7 of 30 patients (23%) in the control group and none in the HBO group. [52] Ducasse and colleagues performed a similar study in 26 non-comatose patients with acute CO poisoning.[53] At 12 hours no patient (0/13) in the HBO group had abnormal clinical findings compared to 5 of 13 in the NBO group. These studies have a number of limitations, the most important being that the authors failed to blind the patients and examiners to the treatment given.43 The studies have, however, highlighted the fact that the optimal benefit from HBO may be obtained when this therapy is offered within 6 hours of intoxication and with at least 2.5 ATM of HBO.

Currently two prospective, randomized, blinded studies are being performed in patients with significant CO poisoning. In both these studies patients are block randomized to normobaric oxygen delivered in a hyperbaric chamber (sham control) and to a hyperbaric group. Interim analyses of both of these studies (with follow up of 73 and 50 patients respectively) have demonstrated no difference in outcome between the NBO and HBO treated groups.[54,55]

There is no agreement amongst toxicologists and emergency medicine physicians that HBO is of benefit, nor the selection of patients who may potentially benefit from this therapy. This issue will not be resolved until the results of the above cited studies are available.54,55 Most advocates of HBO are to be found in specialized treatment centers with ready access to hyperbaric chambers. The implications of recommending HBO for patients in rural areas or cities without chambers cannot be underestimated. Transfer to a distant facility may be impractical or even dangerous, especially if treatment will take place in a monoplace chamber or in a facility without critical care staff and equipment. The cost may have important implications when recommending HBO, since this therapy is 4 to 5 time as expensive as treating a patients with NBO, not including transport costs which may run over $3000 for aeromedical evacuation.

Currently the Undersea and Hyperbaric Medical Society recommend HBO for those patients with signs of serious

intoxication regardless of their COHB levels.[56] This includes patients with a history of unconsciousness, presence of neurological signs, cardiovascular dysfunction or severe acidosis. Pregnant women should be evaluated with liberal criteria for HBO due to the increased toxicity risk to the fetus

In the absence of access to HBO therapy, severe poisoning should be treated with 100% oxygen, with endotracheal intubation in patients who cannot protect their airway. In these patients, consideration should be given to transfusion of packed red blood cells.[57]

VIII. DISPOSITION

Classification of patients based primarily on COHb levels is inappropriate and potentially misleading, as the level alone is a poor predictor of the degree of injury. However, any patient with a COHb level >25% should be carefully evaluated for admission, even if asymptomatic. In cases of less severe poisoning, close observation or hospital admission with 100% O2 administration should be undertaken until the patient is asymptomatic.4

IX. PROGNOSIS

The data regarding prognosis in CO poisoning are also inconclusive and contradictory. Whereas definitive studies are lacking, it appears that roughly 30% of patients with severe poisoning have a fatal outcome.49 One study has estimated that 11% of survivors have long-term neuropsychiatric deficits, including 3% whose neurologic manifestations are delayed.[58] One third of CO poisoning victims may have subtle but lasting memory deficits or personality changes.40

Indicators of a poor prognosis include altered consciousness at presentation, advanced age, patients with underlying cardiovascular disease, metabolic acidosis, and structural abnormalities on CT or MRI scanning.49 The absence of favorable data for patients in whom HBO is initiated more than six hours post discovery, suggests a poor prognosis and should discourage transport to remote HBO facilities if that time period will be exceeded.7

X. CONCLUSION

CO poisoning continues to be a significant health problem both in the United States and many other countries. CO poisoning is associated with a high incidence of severe morbidity and mortality. The history of exposure and COHb levels should alert the physician to this diagnosis acutely. In the absence of exposure history, CO poisoning must be considered when 2 or more patients are similarly or simultaneously sick. The diagnosis must be excluded by a directed history and physical exam. If suspicion remains COHb testing should be done and O2 therapy should be started empirically while results are pending. If CO poisoning is confirmed, the source must be identified and recommendations for correction or avoidance made. Although definitive data are lacking on the efficacy of HBO in this illness, early HBO treatment may have a role in severely poisoned patients.

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