Editorial

Carbon monoxide inhalation poisoning

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- Carbon monoxide (CO)
- Carboxyhemoglobin (COHB)
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SUMMARY. Carbon monoxide (CO) inhalation is a relatively common cause of toxicity, often unnoticed due to non specific clinical presentation. Central nervous system and heart are mainly involved by mechanisms that come from the high affinity of hemo-proteins for CO, leading to hypoxic and peroxidation damage. Diagnosis may require a high grade of suspicion, oxygen supplemental therapy is the main pillar of therapy but supportive measures may be needed, as hemodynamic, respiratory and mental complications can occur. Late neuropsychiatric disorders are possible, for which early hyperbaric oxygen treatment may be of benefit. *Pneumon 2014, 27(1):21-24.*

INTRODUCTION

Carbon monoxide (CO) poisoning is the reason for up to 45.000 emergencies per year in the US and is considered responsible for 5.000-6.000 deaths.[1] Fire incidents and combustion exhaust in inadequately ventilated spaces are the most common situations of serious CO intoxication and death, while some lower level of exposure, leading to milder clinical symptoms, usually is the result of increased atmospheric CO (heavy traffic – industrialized urban environment, occupational exposure).[2] CO poisoning recently enjoys an unwelcome popularity in Greece during the economic crisis, due to the increasing household use of combustion-based heaters (sometimes even improvised), instead of central heating installments or electricity-powered devices.

PATHOGENESIS

The mechanisms of action of CO intoxication involve the classical tissue hypoxia and the, more recently discovered, direct cellular damage of immunological and inflammatory etiology. The hypoxemic effect is the result of hemoglobin's (Hgb) approximately 210–fold higher affinity for CO, compared to O_2. Carbon monoxide lowers blood's O_2 capacity by displacing it from Hgb to form carboxyhemoglobin (COHgb), but also induces an O_2 dissociation curve left shift the of the unaffected oxyhemoglobin (O_2Hgb), thus decreasing further the ability of unloading O_2 to the tissues[3] (Figure 1). This "relative anemia" reduces the oxygen delivery and could cause direct

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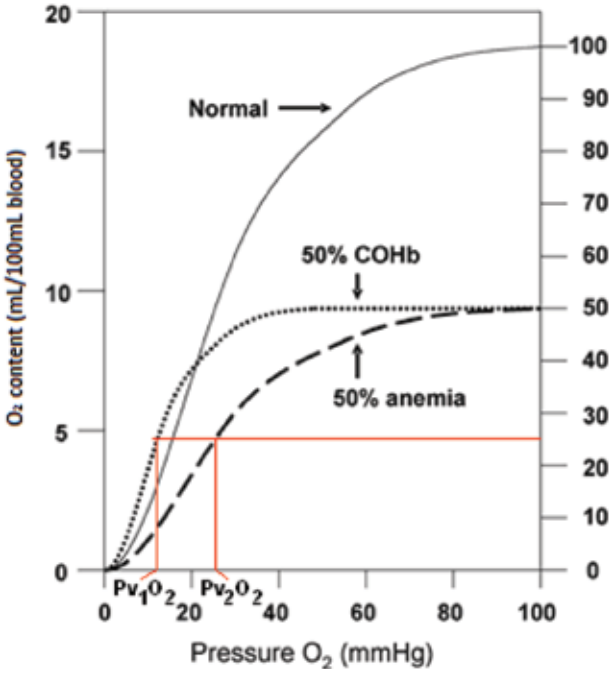

FIGURE 1. The solid line depicts the normal dissociation curve, the dashed line shows the impact of reducing the hemoglobin content by half (anemia) and one (small dotted line) the impact of 50% COHgb. The left shift associated with COHgb demonstrates the extra adverse effect of CO versus merely loss of hemoglobin O_2 carrying capacity. The partial pressure of O_2 when hemoglobin gives up 50% of its available O_2 is at ~16 mm Hg (Pv_1O_2) when COHgb is 50%, versus ~26 mm Hg (Pv_2O_2) when there is a 50% anemia.

hypoxic injury to sensitive organs (i.e., heart and brain). Cellular toxicity from CO poisoning is directly associated with its affinity for other heme-containing proteins, including cytochromes, myoglobin and guanylyl cyclase.[4] As CO binds to cytochromes it compromises energy production at mitochondrial level by free radical mediated mechanisms.[5] Myoglobin binding of CO inhibits the transport of O_2 to the mitochondria that may lead to myocardial and skeletal muscle hypoxia, direct cellular necrosis and rhabdomyolysis.[6] The CNS is affected by CO release at neuronal level, which initiates glutamate over-release, influx of calcium into the cells, free-radical-mediated injury and additional neutrophil activation, with final result lipid peroxidation, neuronal death and demyelination.[7]

CLINICAL PRESENTATION

Brain and myocardium are more sensitive to the effects of CO due to their higher metabolic and oxygen demands. Despite the multiplicity of novel mechanisms proposed to explain the damage made by CO, the direct hypoxemic effect should not be overlooked, mainly in cases of brain injury in subjects with underlying heart and / or lung co-morbidities. Therefore, certain populations (i.e., coronary artery disease, chronic obstructive pulmonary disease) are more vulnerable to the effects of CO and could present symptoms of hypoxia and even death at lower levels of COHgb than generally expected. The symptoms associated with CO poisoning usually begin with headache (>80%), and follow a climax, as the concentration of COHgb rises, that includes dyspnea, chest pain, nausea, vomiting, impaired judgment, visual disturbances, fatigue, confusion, coma, seizures, circulatory and respiratory failure and death. The main symptoms come from the CNS, probably by the hypoxemic effect that leads to increased intracranial pressure and cerebral edema. Although symptoms generally follow the above order in relation to COHgb levels, there is no clear correlation, probably due to the influence of other factors, like co-morbidities, age, duration of exposure and genetic susceptibility.[2]

Besides the acute presentation, a delayed neuropsychiatric syndrome may occur in patients, from 3 up to 240 days after the CO exposure. This happens grossly in unpredicted manner, and although some risk factors have been identified, there is no secure predictive criterion, including the COHgb levels and the seriousness of the acute event. Even those victims without immediate neuropsychological symptoms may demonstrate delayed impairment, ranging from subtle personality changes or mild cognitive deficit to severe dementia, psychosis, parkinsonism, incontinence. Behavioral impairments reported include alterations in attention, executive function, verbal fluency, motor abilities, visual-spatial skills, learning, short-term memory and mood/social adjustment. The late neuropsychiatric sequelae have been shown to occur in up to 50% of the patients with >10% COHgb, they have a mean onset latency of 3 weeks and, generally, have a relatively good prognosis (50-70% remission in one year).[1]

DIAGNOSIS

Carbon monoxide poisoning diagnosis is based on the triad of: 1) recent history of a situation compatible with CO exposure, 2) symptoms consistent of CO poisoning and 3) laboratory finding of elevated COHgb level. There

is no single symptom or a combination of symptoms that may confirm or exclude the diagnosis, the most frequent ones include headache, nausea, vomiting, confusion, fatigue, chest pain, dyspnea, loss of consciousness. "Cherry red" skin or mucous membranes coloring, caused by the brighter shade of red that capillary COHgb has, compared to O_2Hgb, requires a lethal exposure to become evident and therefore should rather be considered a necropsy finding than a valid clinical sign.[8] Clinical suspicion should be raised upon awareness of various, non strictly medical, factors (eg. socioeconomical status, eventual suicide attempt, occupation, seasonal incidence during cold days) as well as frequently related medical situations, such as acute coronary syndrome and arrhythmias. Clinical investigation should include other eventual members of a household that may be in risk of exposure. If the suspected source of a CO poisoning victim is an occupational or residential setting that may endanger public health, civil protection services should be urgently notified.

Clinical diagnosis of CO poisoning should be confirmed by an elevated level of COHgb, either in arterial or venous blood sample. Carboxyhemoglobin levels vary with smoking habit, inhaled air concentration and duration of exposure, time gap from exposure termination to blood sampling, supplemental O_2 therapy before the time of measurement. Normal value of COHgb for non smokers is <2% and for smokers 3-12%. Smokers are usually in the 3-5% range, can rarely exceed 10% and a general rule of 2,5% increase for every pack / day may be used.[8] Environmental air exposure levels considered safe according to WHO range from 87 ppm (100 mg/m^3) for 15 min, to 8,7 ppm (10 mg/m^3) for 8 h, while exposure of any duration to air containing more than 100 ppm is dangerous to human health.[9] The COHgb levels measured at the time of clinical investigation must be interpreted with respect to the half life of CO in blood. Normobaric O_2 at 100% speeds up the displacement of CO from circulating hemoglobin, reducing the $T_{1/2}$ to approximately 75 min, compared to 320 min when breathing room air[10], and it may be furthered lowered to 20 min using hyperbaric O_2 (HBO_2) treatment[2]. A poisoned patient with initial COHgb concentration of 30% breathing normobaric 100% O_2 during a 2 h transportation to emergency department could present a modest 10% or less of COHgb when measured, therefore, obtaining a blood sample early, possibly at the site of poisoning, could be of use when CO poisoning is suspected.

A short comment is necessary regarding the confusion that may arise from measuring COHgb levels and assessing the oxygenation of a CO poisoned patient. First, when interpreting the blood gas analysis, a physician should be able to rule out if the oxygen saturation value reported is a measured or a calculated one. Modern ABG machines typically perform spectrophotometry on injected sample, thus directly measuring the concentrations of oxy-, deoxy-, carboxy- and methemoglobin and they report the corresponding values labeled as measured. Some older models calculate oxygen saturation based upon algorithms that use the dissociation curve and pH, reporting a calculated Sat% value, irrespective of the real amount of COHgb present on the sample. Second, standard two wavelength (660 – 990 nm) pulse oxymeters cannot differentiate oxy- and carboxyhemoglobin, because the two molecules share similar wavelength absorbances. No clinically important difference in the value reported by an ordinary pulse oxymeter will be noted, unless COHgb levels rise to more than 40%, which makes this method unacceptable. Special CO pulse oxymeters are available commercially since 2005 but substitution of blood sampling with non invasive measurement is not recommended for clinical decisions.[8]

MANAGEMENT

The first-line treatment in all cases of CO poisoning is the administration of high fraction of inspired oxygen, using a high-flow non-rebreathing mask, or by mechanical ventilation when the endotracheal intubation criteria are met.[11] The eventuality of intubation and ICU transfer should be assessed, if mental status suggests unprotected upper airway or there is prominent hemodynamic and / or respiratory compromise. Supplemental oxygen accelerates the elimination of CO from the related hemoproteins and alleviates tissue hypoxia. There are no clinical trials in favor of this practice, although, it is reasonable to recommend the administration of high-flow oxygen the sooner possible, even as a pre-hospital care in case of suspected CO poisoning, and until COHgb level normalizes (<3%) and the symptoms are weaned, usually for 6 h.

The use of hyperbaric oxygen (HBO) is a valid alternative to normobaric 100% oxygen (NBO), but the relative inconvenience, limited availability, high cost and logistical problems, practically tend to limit its use. Several studies have addressed the comparison between HBO and NBO, there is no evidence that HBO influences the mortality rate, but there are studies in favor of a better outcome in terms of late cognitive sequelae up to one year after treatment.[8] Risk factors for long-term cognitive impair-

ment in patients not treated with HBO are considered age >36 years, exposure duration >24 h, loss of consciousness and COHgb level >25%.[12] It is recommended to consider HBO within the first 24 h in patients with risk factors, even if they are clinically stable and seem not likely to die because of the CO poisoning.[11] Hyperbaric oxygen treatment is considered safe during pregnancy and is recommended in pregnant women, irrespective of poisoning severity. Optimum dose and frequency of treatment are unknown, in practice these decisions are left to the attending hyperbaric physician, usually patients are treated at 3 atm for up to 3 treatments, if they remain symptomatic.[13]

If the CO exposure is suspected to be an attempted suicide, toxicology exams should be made to screen for eventual use of drugs, chemicals or alcohol. Impaired mental status that is not explained by the CO exposure and / or insists after several hours of supplemental oxygen treatment is highly indicative of co-poisoning.[14] Severe metabolic acidosis (pH <7,20 or plasma lactate >10 mmol/L) is positively correlated with high short-term mortality (30-50%) and, in these cases, concomitant cyanide poisoning is likely, especially when the CO source is a fire incident. Empiric treatment with the antidote hydroxycobalamin is recommended.[15]

Patients with heart disorders are more likely to present features of cardiac ischemia, such as angina, infarction, conduction abnormalities and sudden death. Cardiologic evaluation and monitoring, including work up for myocardial ischemia should be offered to selected patients.[2] All patients surviving a CO poisoning should be scheduled at least one follow up visit 1-2 months after the event to screen for late cognitive impairments. Memory disturbance, depression, anxiety, inability to calculate and motor dysfunction rarely may develop, but studies suggest that mortality rate after an episode of CO poisoning is higher compared with the normal population, fact that may be explained by accidental deaths due to these symptoms. Patients with evidence of cardiac damage should be scheduled for cardiology follow-up and patients with intended exposure should have mandatory psychiatric care.[8]

PREVENTION

It is thought that public education programs designed to increase awareness of CO poisoning and placement of warning labels on commercially used fuels and devices emitting CO could have some effect in reducing the incidence. It should be noted that many of the candidate victims may not be native speakers, so warning signs instead of verbal notes could be more effective. The installment and use of CO alarms in residential or occupational closed spaces could be a valid preventive measure.

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