REVIEW ARTICLE

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Carbon Monoxide Poisoning: Clinical Manifestations, Consequences, Monitoring, Diagnosis and Treatment of Toxicity

SUMMARY
Carbon monoxide poisoning is a multisystem condition that may present with a wide range of symptoms and can cause a confusing constellation of clinical features. Diagnosis may be easily missed if physician is not alert about. Carbon monoxide intoxication is more frequent than it is reported. It has a simple treatment if diagnosed, and has many long-term sequela if under-treated.
Keywords: Carbon Monoxide, Poisoning, Carboxyhemoglobin.

Karbon Monoksit Zehirlenmesi: Klinik Bulgular, Sonuçlar, İzlem, Zehirlenme Tanısı ve Tedavisi

ÖZ
Karbonmonoksit zehirlenmesi, birçok sistemi etkileyen, geniş bulgular yelpazesi ile hekim karşısına gelebilen bir durumdur. Klinik prezantasyonun değişken olması, hekimin karbonmonoksit zehirlenme vakasını gözden kaçırmasına olabilir. Toplumda karbonmonoksit zehirlenmesi olguları kayıtlarda gösterildiğinden daha fazladır. Teşhis edilmesi halinde basit tedavi yöntemleri ile tedavi edilebilir ve uzun dönem sekelleri azaltılabilir bir durumdur.
Anahtar Kelimeler: Karbon Monoksit, Zehirlenme, Karboksihemoglobin.

CARBON MONOXIDE: IDENTIFICATION, STRUCTURE, AND SOURCES

Carbon Monoxide (CO) has been used since prehistorical time to melt the iron and other metals. It also was used for executions by the Greek and Romans in antique time. And the first chemical description of the gas was by Spanish doctor Arnaldus de Villa Nova in the 11th century. The gas was identified as a compound containing carbon and oxygen by the Scottish chemist William Cumberland Cruikshank in the year 1800. Its toxic properties on dogs were thoroughly investigated by Claude Bernard around 1846 (1,2). Later, in 1857, Bernard first described the toxic effects of, and in 1895, Halder described the underlying mechanism of CO toxicity (3).

CO is a natural molecule in human body, up to a certain level; it is a product of hemoglobin degradation and results in baseline carboxyhemoglobin (COHb) saturation of 1-3% in non-smokers and 5-10% in smokers. Though heme oxygenase and heme oxygenase-like activity is the predominant source in mammals, oxidation of organic molecules is another minor source of intrinsic CO. Carbon monoxide is produced by incomplete combustion of hydrocarbons; charcoal, wood, kerosene, or natural gas used for heating and cooking. According to ten years review of carbon monoxide related deaths in USA, more than half of unintentional deaths were caused by motor vehicle exhaust (4). Carbon monoxide is a 'silent killer' that leads to multiple human deaths each year, as a result of a home accident or disaster.

Epidemiology of carbon monoxide poisoning

CO poisoning is the leading cause of poisoning deaths (accidental and intentional) in the United States (5). In fact recorded numbers of CO-related deaths are grossly *under-reported* cases or are mainly misdiagnosed by medical professionals. Therefore, precise number of fatal CO poisoning is not known exactly (6). According to a demographic study on pediatric accidents, the fatal CO poisoning ratio in children is 1% of total accidents (7). CO poisoning, is also an occupational disease and highly observed among traffic policemen, heating employee, and motor industry workers (8). There are many studies on pregnant smokers, showing developmental harmful effects of CO on babies during pregnancy (9) Fatal death frequently occurs in severe CO poisoning (estimated fetal mortality is up to 36-67%) (10), because placenta delays fetal detoxification and also because fetal hemoglobin has greater affinity for CO than adult hemoglobin (3). Besides, some studies show that even one-time intrauterine exposure to CO may lead to intrauterine hypoxia, fetal brain damage and increased fetal death (11). In our country, the number of CO poisoning is also high because of inappropriate ventilation in indoor areas and domestic stoves (6,12,13).

How does CO works? The pathophysiology

Inhaled CO rapidly switches the alveolar capillary membrane and enters intravascular area. Here, CO binds respiratory pigments (hemoglobin, cytochrome P450 and cytochrome aa3) with high affinity. CO also binds other iron-containing proteins; myoglobin, cytochrome, neuroglobin. CO and O_2 races competitively for Hb (2,3,6).

Co effects organism in different ways (2, 5, 14);

1. *CO binds Hb* (with a higher affinity up to 200-300 times) and forms COHb molecule. It prevents oxygen transport and release to tissues. *Thus, it results in relative anemia, tissue asphyxia and hypoxia.*
2. *CO causes structural changes on Hb molecule*, and makes it difficult to provide oxygen for tissues.
3. CO disrupts mitochondrial functions by binding cytochrome-c oxidase. *Thus disrupts oxidative phosphorylation, reduces cellular respiration and causes cellular hypoxia.*
4. CO binds myoglobin, also with a high affinity, up to 20-50 times. *It leads to myocardial depression and hypotension by causing tissue hypoxia*.
5. *COHb increases the adhesion of white blood cells to endothelial surfaces, especially in brain tissue.* CO causes leukocyte-dependent inflammatory changes and lipid peroxidation in the brain and leads to white matter demyelination edema and focal necrosis, also *causes reperfusion damage*.
6. CO binds muscle myoglobin, reduces O_2 pressure and *leads to rhabdomyolysis.*

Clinical presentation and prognosis of CO intoxication

Considering the mechanism mentioned earlier CO may have different presentations. Clinical manifestations include almost all systems, have a wide range of symptoms, lead to various systemic complications and sequels, and are associated with asphyxia due to inhibition of oxygen transport of Hb. The blood and tissue COHb levels and duration of the exposure determine the symptoms. Severity of symptoms varies from person to person, however there may not be a clinical correlation between CO levels and severity of the presentation. Again *some special groups in population are at greater risk and are more vulnerable* to *the toxicity; children, the elderly, patients with pulmonary and heart disease, individuals living in high areas, smokers and individuals with high CO levels.*

Physicians should be aware of carbon monoxide intoxication, especially during the

winter, when risk of continued prolonged exposures may be greater. Occupation should be questioned, and all patients presenting with flu-like symptoms (such as headache, nausea, dizziness) should be investigated in case of CO exposure. Table 1 shows some criteria for admission and prolonged observation of such cases (2).

Table 1. Criteria for prolonged observation (1)

1.	Loss of consciousness.
2.	Neurological deficit at any time.
3.	Clinical or electrocardiographic signs of cardiac compromise.
4.	Metabolic acidosis.
5.	Abnormal chest radiograph.
6.	COHb level >25%, COHb level >15% with a history of cardiac disease or > 10% in a pregnant patient.
7.	PO<60 mm Hg.

The brain and the heart are organs with high O_2 consumption, so the main findings of CO poisoning are cardiovascular and neuropsychiatric symptoms(14). Table 2 illustrates the incidence of clinical presentation in CO poisoning (6).

Table 2. The incidence of clinical symptoms (5)

• Headache	91%
• Dizziness	77%
• Fatigue	53%
• Nausea	47%
• Cognitive impairment	43%
• Dyspnea	40%
• Visual impairment	25%
• Chest Pain	9%
• Loss of consciousness	6%
• Abdominal pain	5%
• Cramps in the muscles of	5%

Considering such a wide range of clinical manifestations it is obvious that differential diagnosis of CO poisoning includes a wide variety of clinical entities. Conditions, CO poisoning can be confused with are cerebrovascular diseases, headaches, meningitis, encephalitis, parkinsonism, heart attack, arrhythmias, drug overdoses, ethyl alcohol and ethylene glycol poisoning, anxiety and depression, acute confusion and hyperventilation syndrome, viral infections, gastroenteritis and food intoxications, acute abdomen and cranial traumas (15).

The symptoms of poisoning may occur in the early period or weeks later, as well. The symptomatology may take two forms: monophasic form, in which survival may range from hours to years, but without remission of symptoms, and the biphasic form, in which there is a period of normality (lucid interval) lasting 1 week to 1 month, followed by a period of chronic abnormalities (3).

The Threshold Limit Value (TLV) of CO is 50 ppm, the maximum allowable concentration of CO is 0.01% (100ppm) for 8-hour exposure and 0.04% (400 ppm) for 1-hr exposure (16). Not only blood concentration of COHb but also duration of exposure determines the time of onset and intensity of the symptoms (16). *It has been shown that low dose but long lasting exposure to CO may lead to more severe long-term toxicity than acute high-dose exposure* (17). Table 3 illustrates signs and symptoms at various COHb concentrations (3).

Choi et al have summarized the literature about the symptomatology, and both acute and long-term effects of CO toxicity, it is one of the most comprehensive clinical reviews in the literature, about systemic manifestations and complications of CO poisoning. The systemic clinical manifestations and complications of CO poisoning are listed in Table 4 (3).

Once CO poisoning occurs, there are some findings defining *poor prognosis*; the *elderly, the duration of exposure, the time period before initial treatment, comatose state, metabolic acidosis, increase in serum amylase and aspartate aminotransferase levels.*

Table 3. Signs and symptoms at various concentrations of carboxyhemoglobin (2)

Saturation of blood COHb	Duration of exposure	Signs and symptoms
0-10%	Indefinite	None
10-20%	Indefinite	Tightness across forehead, slight headache, dilatation of cutaneous vessels
20-30%	5-6 hr	Headache, throbbing in temples
30-40%	4-5 hr	Severe headache, weakness, nausea, vomiting, dimness of vision, dizziness, collapse, cherry-red color of lips and skin.
40-50%	3-4 hr	As above, plus; syncope, increased pulse and respiratory rate
50-60%	11/2-3 hr	Tachycardia, tachypnea, Cheyne-Strokes respiration, coma, convulsion.
60-70%	1-11/2 hr	Coma, convulsion, decreased heart action and respiration, possibly death.
70-80%	1-2 min	Weak pulse, depressed respiration, respiratory fairly and death.

Table 4. Systemic clinical features and complications of CO poisoning (2)

System	Clinical findings
Cardiovascular	ECG changes (T wave and ST segment), cardiomegaly, angina pectoris, myocardial infarct, tachycardia, bradycardia, A-V block, atrial fibrillation, premature ventricular contraction, ventricular fibrillation, shock.
Respiratory	Pneumonia, pulmonary edema, adult respiratory distress syndrome
Genitourinary	Glycosuria, proteinuria, hematuria, myoglobinuria, acute renal failure, abortion, still-birth, menstrual disturbance, reduction in weight of testes and in number of spermatozoa
Gastrointestinal	G-I disturbance, G-I bleeding, gastric ulcer, hepatomegaly
Hematological	Leukocytosis, erythrocytosis, anemia, pernicious anemia, thrombotic thrombocytopenic purpura
Metabolic and endocrinological	Hyperglysemia, decreased T_3, acute hyperthyroidism
Dermatological	Bulla, erythema, swelling, ulcer, gangrene, alopecia
Musculosceletal	Muscle necrosis, Volkman's contracture, osteomyelitis
Ophtalmological	Retinal hemorrhage, papilledema, retinopathy, optic atrophy, amblyopia, scotoma, hemianopsia, blindness
Otologic	Disturbance of cochlear and vestibular functions

Diagnosis of poisoning and detection of the toxicity

The first and the most important step in diagnosing CO poisoning is to suspect the patient may have CO poisoning and to take a goal-directed history. The diagnostic value of physical examination is limited.

The only specific method in diagnosing CO poisoning is spectrophotometric or chromatographic detection of blood COHb. While a hand held breath analyzer can be used to quickly rule out carbon monoxide poisoning, physicians must know that high levels of COHb are significant, but low levels of it do not exclude the poisoning. The basic blood COHb levels in heavy smokers, in those with chronic lung diseases and persons extensively exposed to automotive exhaust gases may range up to 8-10%. Symptoms often begin between concentrations of 10-30%, while persons who succumb may have postmortem blood levels of 30% to 90% (18).

The other methods *that can be used* for detecting CO toxicity are:

- Arterial blood gas analysis- metabolic acidosis (which may occur secondary to lactic acidosis that is a result of ischemia) can be detected. Arterial PaO_2 and PCO_2 pressures are usually normal. O2 saturation is at normal levels**,** too, but it does not reflect the actual tissue hypoxia.
- Electrocardiography (ECG) – Biphasic T waves, T wave inversion and sinus tachycardia are the most common ECG findings(19). Ventricular fibrillation, and cardiac arrhythmias in general, constitute the major life-threatening condition**s** during acute exposure (3).
- Complete blood count- Hemoglobin and hematocrit may be elevated, mild leukocytosis, disseminated intravascular coagulation and thrombotic thrombocytopenic purpura may develop (20).
- Biochemical parameters-
  - *Creatinine kinase (CK), creatinine kinase-MB (CK-MB) and troponin should be determined* (even as minor as 5-10% increase in COHb levels may trigger angina in persons with heart disease and even may depress myocardium in healthy people. So in order to be alert about silent ischemia these markers should be determined (6)).
  - *Myoglobin and lactate dehydrogenase* increase in cardiac injury and Rhabdomyolysis (20).
  - *Blood electrolytes and glucose* (hyperglycemia, hypokalemia and lactic acidosis may occur in severe poisoning).
  - *Kidney function tests* should be determined (acute renal failure may occur secondary to ischemia, muscle necrosis and myoglobinuria, and it is a potentially fatal complication of CO poisoning (20)).
  - *Liver function tests* (to avoid fulminant hepatitis).

  Studies on new markers for CO poisoning are being held on (21).
  - Urine test – Glycosuria, proteinuria, hematuria, and myoglobinuria also can be seen (3).
- Imaging;
  - Chest X-ray- Patients with pulmonary symptoms must undergo chest X-ray. Chest X-ray mostly shows no abnormality, the most common

pathological features of the lung are pneumonia, ground glass appearance and pulmonary edema (22), which indicate poor prognosis.

- Computed tomography (CT) – Patients with mental alterations should undergo cranial CT. The most characteristic CT finding of CO toxicity is hypodense lesions with focal necrotic areas in basal ganglia, and especially symmetric density reduction in globus pallidus and substantia nigra. Cerebral edema is observed in severe intoxications (23).
- Magnetic resonance imaging (MRI) – MRI is superior to CT in detecting CO induced brain damage. Subcortical white matter hypodensities, cerebral cortical lesions, hippocampal lesions, and loss of gray-white differentiation may be observed (24).

- Electromyography (EMG) – Peripheral neuropathy following CO exposure is also a quite common entity; it is common in young adult, lower extremities are the most-vulnerable body parts, and is usually associated with local swelling due to muscle necrosis (25). EMG usually demonstrates diffuse slowing but it is of little diagnostic value.
- Single photon emission computed tomography (SPECT) - It has also been used in CO poisoning cases, but rather used in detecting long-term sequels.

Management of CO poisoning

The main goal of treatment is to increase oxygen delivery to vital organs. Treatment should be guided by clinical symptoms rather than COHb levels, because, as it was discussed previously, COHb levels do not always correlate with severity of the presentation. If necessary, basic and advanced life support must be provided, coma and convulsions should be treated.

In case of pregnant patient, fetus must be monitored. Accumulation of CO in fetal blood is 10-15% higher than in maternal blood, and partial O_2 pressure is 20-30 mmHg lower. While half-life of COHb in normal room air is 3-4 hours, this time is 6-7 hours in fetus (6).

Of course exposure sources must be controlled and cleaned, and the patient must be decontaminated.

Physical exercise of the patient must be kept to a minimum in order to reduce the oxygen requirement. It is necessary to limit physical activity for about 1-3 weeks after intoxication. Considering that long term neurological effects can manifest themselves later, and that recovery can take up to 20 days, the patients should be called for controls in the second and fourth weeks (15,26).

Antidotal treatment of CO intoxication bases on simple O_2 supplement in order to quickly clear COHb from the blood and to reduce the half-life of COHb (from about 4-5 hours to 1 hour). A simple non-rebreathing oro-nasal mask at a flow rate of 6-10 liters/minute with 100% oxygen is the first option in the treatment (15). Studies show that if treatment with oxygen at 1-atm pressure is applied within first 6 hours after poisoning, mortality declines from 30% to 10%, and neurological sequels reduces significantly (27).

Patients with mild symptoms and with findings that decline after 6-hour of oxygen therapy could be discharged. Patients should be called for re-evaluation immediately~~,~~ if symptoms renew, and 24-48 hours later if not. At the control visit the ECG, systemic examination and evaluation of myoglobinuria is recommended (15).

Table 5. Indications for HBO therapy in CO poisoning (1)

1.	Comatose patients.
2.	Any period of unconsciousness.
3.	Patients with severe acidosis.
4.	Patients >60 years old.
5.	Any abnormal score on the Carbon monoxide neuropsychological screening battery.
6.	Patients with COHb levels >40%.
7.	Cardiovascular involvement (chest pain, ECG changes arrhythmias).
8.	History of ischaemic heart disease and COHb levels >15%.
9.	Pregnant patients with COHb levels >15%.
10.	Patients who do not respond to 100% oxygen after 4 to 6 h.
11.	Patients with recurrent symptoms up to three weeks after exposure.

What is hyperbaric oxygen treatment, when and why?

Oxygen therapy can be both normobaric (NBO) and hyperbaric (HBO). HBO is defined as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurized to a pressure greater than that of sea level (28). Hyperbaric oxygen therapy for carbon monoxide intoxications was first discussed by Haldane in the 1890s and was first used in the 1960s (29).

The half- life of CO is 250 min. This time shortens up to 50 min at sea level (NBO) and up to 22 min at 2.5 atm pressure (HBO) (6). Additionally, when breathing normobaric air, arterial oxygen pressure is approximately 100 mmHg, and tissue oxygen pressure is 55 mmHg. However, 100% oxygen at 3 atm can increase arterial and tissue oxygen pressure up to 2000 mmHg, and 500 mmHg, respectively. Thus, approximately 60 ml soluble oxygen per litre of blood is delivered to tissue**s** and supports the tissue even without contribution from haemoglobin. Both facilitating the elimination of COHb and increasing the level of

soluble O2 in the blood are the main mechanisms of HBO therapy (28).

Despite this knowledge there is no clear consensus on benefit of HBO therapy in CO poisoning, as there are many studies illustrating both recovery after HBO and no difference in CO caused sequels.

Indications for HBO therapy in CO intoxication cases are listed in Table 5 (2). Of course**,** there are some relative**s** risks in HBO treatment, such as cardiac or pulmonary disease but the only absolute contraindication to HBO is untreated tension pneumothorax, and it must be excluded before the treatment (28).

In conclusion, Carbon monoxide poisoning is a multisystemic condition that may present with a wide range of symptoms and can cause a confusing constellation of clinical features. Diagnosis may be easily missed if physician is not alert about. CO intoxication is more frequent in population than is reported. It has a simple treatment if diagnosed, and have many long-term sequels if is under-treated.

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