Review
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Carbon Monoxide Poisoning

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Abstract

Carbon monoxide (CO) is an odorless, colorless and tasteless poisonous gas with a molecular weight similar to air in low concentrations. For this reason, CO, which is also defined as the "silent killer", is one of the most common causes of fatal poisoning. Mortality depends on the duration of exposure to CO and its concentrations. Carbon monoxide poisoning, is still among the leading poisonings in the world. Whether it is for suicidal purposes or as a result of accident, it is a preventable, important cause of morbidity and mortality. In this review, it is aimed to review the pathophysiology, causes, diagnosis, treatment, prognosis and complications of CO poisoning. It has been tried to explain what needs to be done in diagnosis and treatment, and current treatment approaches.

Keywords: Carbon monoxide, poisoning, emergency

Özet

Karbon monoksit (CO), düşük konsantrasyonlarda havaya benzer moleküler ağırlığa sahip kokusuz, renksiz ve tatsız zehirli bir gazdır. Bu nedenle "sessiz katil" olarak da tanımlanan CO, en sık ölümcül zehirlenme sebeplerindendir. Ölüm oranı, CO'ya maruz kalma sürelerine ve konsantrasyonlarına bağlıdır. Karbon monoksit intoksikasyonu halen dünyada ön sıralarda yer alan zehirlenmeler arasında yer almaktadır. Gerek suisidal amaçlı, gerekse kaza sonucu olsun, önlenebilir, önemli bir morbidite ve mortalite sebebidir. Bu derlemede CO zehirlenmesinin patofizyolojisi, nedenleri, tanısı, tedavisi, prognozu ve komplikasyonlarının gözden geçirilmesi amaçlanmıştır. Tanı ve tedavide yapılması gerekenler, güncel tedavi yaklaşımları anlatılmaya çalışılmıştır.

Anahtar Kelimeler: Karbon monoksit, zehirlenme, acil

Introduction

Carbon monoxide (CO) is formed when hydrocarbon-based fuels and materials are not completely burned. The poisonous gas is formed when an oxygen and a carbon atom bond. It is known as the silent killer because it is colorless, tasteless and odorless. It is formed by the combustion of fuels such as natural gas, coal, wood used in heating, tobacco smoke, the burning of energy sources used in factories and motor vehicles. In addition, volcanic eruptions, forest fires and the emission of gases also cause the formation of CO[1].

It is one of the most abundant air pollutants, so every individual is exposed to CO by breathing on a daily basis. However, small amounts of CO are produced endogenously, mainly through the catalysis of heme and heme-containing proteins, and processes such as lipid peroxidation and photooxidation. Therefore, very low amounts of endogenous CO are found in each individual, but their levels can vary with physiological as well as pathological conditions[2]. Indoor CO concentrations in the air are below 30 ppm, about twice the amount in open air[3].

Although the World Health Organization (WHO) and national health and safety agencies have clear guidelines on tolerance limits for CO exposure, this poisoning is the main cause of non-fire-related accidental poisoning deaths in most countries[4].

Carbon monoxide; It is 10-15% bound to proteins such as myoglobin and cytochrome oxidase, but less than 1% is soluble in plasma. This causes tissue hypoxia. As a result, all systems are affected, especially respiratory, peripheral, central nervous system and cardiovascular system. Clinical findings vary according to the systems involved[5].

The clinical diagnosis of CO poisoning is difficult due to nonspecific symptoms[5]. It has symptoms such as fatigue, headache, dizziness, nausea. The causes of CO poisoning are attributed to other diseases and are misdiagnosed[6].

The management of CO poisoning primarily consists of symptomatic treatment and oxygen therapy. Hyperbaric oxygen (HBO) therapy is usually available for more severe cases in a pressurized chamber. Although HBO therapy reduces carboxyhemoglobin (COHb) half-life[7], its advantages are still questioned due to the lack of

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conclusive evidence that it improves survival and reduces morbidity[8,9].

Pathogenesis

From the lungs, CO passes into the blood through the alveoli. Reversible binding occurs at the same iron atom on the heme site where oxygen binds; the product of this binding is COHb. The affinity of CO for hemoglobin is 230-270 times greater than that of oxygen[10]. Carbon monoxide can cause toxicity even at low concentrations. In the case of poisoning, the oxygen-hemoglobin dissociation curve shifts to the left and the release of oxygen to the tissues is prevented[11]. Oxygen uptake by the tissues is impaired and the oxygen capacity that can be carried in the blood decreases. This condition is called "chemical anemia" or "anemia-like effect"[12]. Ten percent of the absorbed CO is bound to myoglobin and cytochrome c oxidase, while less than 1% dissolves in plasma[13]. Exposure duration, respiratory functions, oxygen concentrations, partial CO in the environment and ventilation of the environment are important in the course of the clinical picture in CO poisoning[14]. The basis of the pathophysiology of poisoning is that CO forms a bond with cytochrome c oxidase, myoglobin, and nitric oxide synthetase apart from hemoglobin and causes direct cellular damage[15]. Carbon monoxide binds with high affinity to cardiac myoglobin and has approximately 40 times greater affinity for myoglobin than oxygen. Carboxymyoglobin causes a shift to the left[11]. In other words, it is carbon monoxide that binds to the mitochondrial cytochrome system and impairs oxidative phosphorylation. This change causes a decrease in oxygen carrying capacity, impaired oxygen release at the tissue level, and cellular hypoxia. Carbon monoxide poisoning can cause signs ranging from contractile dysfunction, heart rate changes, mild and temporary cardiac damage to necrosis. This causes a further deterioration in oxygen use in the heart and muscle tissue. Cardiac contractility and output decrease the oxygen required for aerobic metabolism as a result of the higher affinity of CO binding to cardiac myoglobin. This may be responsible for cardiac dysfunction and arrhythmia[7]. Oxygen transport to peripheral tissues is further reduced. Carbon monoxide disrupts the mitochondrial respiratory chain at the level of cytochrome c oxidase, decreases the glutathione level and is directly toxic to mitochondria[10]. While cytochrome c oxidase has a low affinity for CO, it has a higher affinity for oxygen and binds to CO in severe hypoxia[16]. As a result of CO poisoning, skeletal muscle may be damaged and acute tubular necrosis, cellular ischemic necrosis and rhabdomyolysis may develop[17]. Carbon monoxide increases transcapillary leakage, lipid peroxidation and free radical formation in plasma, and increases leukocyte sequestration at the endothelial surface[18]. The brain is also very sensitive to the toxic effects of CO. The main mechanism in CO-related brain injury is hypoxia due to COHb formation. Ischemic and anoxic brain injuries are caused by a decrease in oxygen transport and mitochondrial oxidative phosphorylation. Causes cognitive deficits in survivors[19]. To ischemic brain damage; it can cause depolarization, oxidative stress, inflammation, acidosis, ionic imbalance and apoptosis. Decreased oxidative phosphorylation and ATP (adenosine triphosphate) synthesis due to inactivation of Ca ATP'ase increases brain damage[20]. Mitochondrial membrane depolarization, neurotransmitter release and cell death occur due to the activation of lipases and proteases in the cell as a result of the decrease in ATP[20]. Cellular dysfunction and increased apoptosis activate glutamate N-methyl D-aspartate receptors[11]. The increase in NO release occurs when CO binds to hemoproteins in platelets and enters into competitive competition with nitric oxide (NO). It produces peroxynitrite, which worsens tissue hypoxia and further impairs mitochondrial function[7,12]. Activated platelets can stimulate neutrophil degranulation and myeloperoxidase (MPO) release. Myeloperoxidase; it increases the inflammatory effects as a result of further degranulation, adhesion and neutrophil activation. The formation of free oxygen radicals is thought to be caused by proteases released from neutrophils by oxidizing xanthine dehydrogenase to xanthine oxidase in endothelial cells[21]. Neurological and cardiac injuries from CO poisoning contribute to the inflammatory cascade.

Clinic

In CO poisoning, patients may present with non-specific complaints. The diversity of clinical complaints is one of the most challenging aspects of making the diagnosis. Patients with CO poisoning may present with different clinical pictures ranging from headache and flu-like complaints to hemodynamic deterioration and profound mental status changes. A high level of suspicion is important for the disease. A detailed history is very important in diagnosing CO poisoning. CO poisoning should be considered in patients brought from a motor vehicle working in closed garages (mostly in non-accidental poisonings) or from burning buildings. There may be a gas leak that the patients working in the workplace with a dangerous gas environment are not aware of, or a leaky natural gas pipe may be present in those who are poisoned at home. In these cases, clues should be sought in the patient's history, such as headaches that resolve after leaving the workplace or home, and behavioral changes.

During CO heme catabolism, it does not endogenously produce more than 1% COHb. Certain disease states, such as hemolytic anemia or severe sepsis, can lead to 3-4% COHb levels as a result of hemoglobin breakdown[22]. Carboxyhemoglobin levels above 10% in smokers and over 2% in non-smokers are considered abnormal and can lead to clinical findings[28]. The first symptom that starts when COHb levels reach 10% is headache. Usually the clinical picture is

Table 1: Carboxyhemoglobin (COHb) saturation (%) levels and symptoms

CO-Hb (%)	Clinical symptoms
< 1	normal range (due to endogenous production)
< 10	smoker's blood (no symptoms)
10–20	fatigue, headache, tinnitus
20–30	fatigue, nausea, vomiting, headache,
30–40	severe headache, nausea, vomiting, dizziness
40–50	syncope, confusion, increased respiration and heart rate
50-60	coma, convulsions, depressed breathing
60–70	coma, convulsions, cardiopulmonary depression, often fatal
70 <	respiratory failure, death

not correlated with COHb levels[10].

Clinical symptoms and signs; it was found to depend on the duration of exposure to CO, its concentration, number of minute ventilations, metabolic rate, and hemoglobin concentration[24]. CO poisoning affects many systems, primarily the heart, kidney, skeletal muscle, peripheral and central nervous system. In CO poisoning, signs and symptoms may appear quickly, or they may appear days or weeks later. Hearing disorders and chest pain can be seen in the late period[10]. Since the oxygen consumption of the brain and heart is high, cardiovascular and neuropsychiatric symptoms occur in the early period[25].

It has been reported that CO poisoning, findings vary according to COHb levels, and this relationship is shown in Table 1.[26]:

In CO poisoning, delayed neurologic syndrome (DNS) may develop 7-240 days later. Personality changes, dementia, memory loss, behavioral disorders, learning difficulties, parkinsonism, attention and concentration disorders, apraxia, psychosis, paralysis, chorea, incontinence or peripheral neuropathy may be observed in these patients[13]. Delayed neurologic syndrome is more common in patients with more pronounced initial symptoms, and 75% of patients recover without additional specific treatments[5]. The systems and clinical findings seen in patients with CO poisoning are shown in Table 2[25].

An increase in cardiac output is seen to compensate for the cardiotoxic effect caused by myoglobin to which CO binds with its high affinity. The main manifestations of cardiac involvement are dysrhythmia and ischemia. Aspiration, heart failure, and hypoxia secondary to pulmonary edema and depression of the central nervous system are other common manifestations[24]. Carbon monoxide intoxication causes ventricular fibrillation as well as lowers the malignant ventricular arrhythmia threshold and may lead to early death[27]. Carbon monoxide poisoning can cause atrial and ventricular fibrillation, premature atrial and ventricular contractions, ST-T wave changes[34], supraventricular tachycardia, QT prolongation[29]. In CO poisoning, drugs that cause QT prolongation should be avoided; because there are studies showing a correlation between prolongation of the QT interval and CO levels[29].

Table 2: The symptoms and clinical findings seen in patients with CO poisoning.

SYSTEM	CLINICAL FINDINGS
Cardiovascular System	ECG changes, tachycardia, bradycardia, cardiomegaly, angina pectoris, premature ventricular contraction, myocardial infarction, A-V Block, atrial fibrillation, ventricular fibrillation, shock
Central and Peripheral Nervous System	Agitation, cerebral edema, behavioral disorders, cognitive impairment, ataxia, muscle rigidity, parkinsonism, peripheral neuropathy, psychosis, memory disorders, personality changes, fecal and urinary incontinence, coma, convulsions,
Genitourinary System	Acute renal failure, glucosuria, proteinuria, hematuria, myoglobinuria, menstrual disorders, stillbirth, abortion, decreased sperm count and testicular size,
Gastrointestinal (GI) System	Hepatomegaly, gastrointestinal bleeding, gastric ulcer,
Hematological System	Pernicious anemia, erythrocytosis, leukocytosis, thrombotic thrombocytopenic purpura
Endocrine System	Acute hyperthyroidism, hyperglycemia, decreased T3 level
Dermatological	Gangrene, bullae, alopecia erythema, blisters, ulcer
Musculoskeletal System	Valkman's Contracture, muscle necrosis, osteomyelitis
Otological Ophthalmological Cochlear and vestibular system disorders	Retinopathy, blindness, retinal hemorrhage, papilledema, optic atrophy

Although the coronary arteries are normal in patients with CO poisoning, left and right ventricular dysfunction may occur. Patients suspected of being exposed to CO poisoning, electrocardiogram (ECG) changes, cardiac marker elevation, existing symptoms, or known left ventricular dysfunction should be evaluated, including echocardiogram, myocardial perfusion scintigraphy, and coronary angiogram[28].

More specific symptoms of chronic CO exposure include dizziness, chronic fatigue, abdominal pain, paresthesias, polycythemia, diarrhea, and recurrent infections[30].

Diagnosis

The most important criterion in diagnosis is the patient's history. As the symptoms are not specific in 30% of the patients, they can be overlooked[13]. Failure to recognize CO poisoning can lead to cardiovascular morbidity, delayed neuropsychiatric sequelae, and mortality due to continued exposure to a hazardous environment. Therefore, with a high degree of suspicion, careful history and timely treatment, significant improvement is achieved in the treatment of patients with CO poisoning. In these patients, the COHb level is not important in the evaluation of the clinical course. In fact, there are studies stating that laboratory results may not be helpful in diagnosing CO poisoning[31]. However, there

are also studies stating that intoxication should be considered as severe in patients with high lactate levels and low pH[32].

Diagnosis of acute CO poisoning usually depends on 3 factors:

1. History of possible exposure to a CO source,
2. Presence of symptoms consistent with CO poisoning,
3. COHb levels greater than 5% in nonsmokers or more than 10% in smokers[34].

Other considerations in fire situations are other toxic gases (such as cyanide and phosgene) and the lack of oxygen from oxygen consumption during combustion. Since cyanide is detoxified by binding to methemoglobin (MetHb), attention should be paid to the concentration of MetHb in the patient's blood when assessing toxicity. Therefore, COHb, cyanide and MetHb should be measured in cases where fire is suspected[35].

In cases of automobile exhaust gas inhalation, inhalation of nitrogen oxide leads to the production of MetHb, which needs to be considered in addition to COHb. Although methemoglobinemia is not common, high MetHb concentrations have been reported in some cases[36].

Tachycardia, hyperthermia and tachypnea, hypertension or hypotension may be present. Strawberry color on the skin, which is a classic finding, is rare. Pallor is more common. Bright red retinal veins (which is a sensitive early finding), retinal hemorrhage in the form of flame burn, homonymous hemianopsia, papilledema can be seen in the eye. Pulmonary edema can be seen as noncardiogenic. Metabolic acidosis may occur secondary to lactic acidosis due to ischemia. Myocardial involvement may also occur frequently as a result of CO exposure. Even 5-10% increases in COHb levels can trigger post-exercise angina in people with a history of coronary disease. However, even in young and healthy individuals, high levels of COHb can depress the myocardium. Sinus tachycardia is the most common ECG finding. Myocardial ischemia, infarction and arrhythmias can be seen secondary to hypoxia. , Electrocardiogram changes can be seen in patients with cardiovascular disease, even if the COHb level is low[37].

Electrocardiogram, troponin, creatine kinase (CK), and creatine kinase-MB (CK-MB) levels should be measured to avoid missing silent ischemia. Myoglobin and lactate dehydrogenase are increased in cardiac injury and rhabdomyolysis. Moderate leukocytosis may occur with CO exposure. Since thrombotic thrombocytopenic purpura and disseminated intravascular coagulation may develop, investigations and total blood count should be performed. In severe poisonings, hyperglycemia, lactic acidosis, and hypokalemia may occur. Therefore, glucose and electrolyte should be checked. Since acute renal failure may develop secondary to myoglobin, renal function should be evaluated[30]. There may be an increase in liver function tests in favor of fulminant hepatitis. Since glucosuria and proteinuria may also be present in chronic poisoning, urinalysis should be performed.

Imaging methods

Lung X-ray imaging should be performed in patients considered for HBO therapy. Although rare, ground-glass appearance, peribronchial cuff findings, intraalveolar edema or perihilar fullness findings can be seen on imaging, and these are indicators for poor prognosis.

Brain tomography (CT): it is not helpful in diagnosis. It can be used in differential diagnosis[13]. Basal ganglia are prone to toxic metabolic abnormalities and systemic disease processes. The most characteristic finding is the presence of focal hypodense lesions in the basal ganglia[38]. Involvement in the cerebellum and brain stem is less common[39]. Diffuse hypoxic encephalopathy, focal cortical damage, diffuse brain atrophy, and white matter demyelination may be seen[40].

Magnetic resonance imaging: it is far superior to CT. Pathological changes in the brain are spongy necrosis of the cerebral cortex, necrosis of the globus pallidus, demyelination of the cerebral white matter, and necrosis of the hippocampus[39].

Treatment

Early diagnosis and treatment have a very important role in the prognosis in suspected CO poisoning. In principle, the diagnosis of CO poisoning is based on clinical symptoms and suspected or confirmed exposure[34].

If possible, treatment should begin in the area of intoxication. The patient should be immediately removed from the polluted area of the poisoning and moved to an environment with fresh air. The patient should be started to breathe 100% O2 quickly with a reservoir mask and supportive treatment should be given[41]. In order to provide 100% O2 to the patient, O2 should be inhaled at 15 L/min with a non-re-breather mask or an O2 mask with a reservoir. It has been reported that the half-life of CO is 320 minutes with fresh air breathing, 74 minutes with 100% O2 respiration, and 20-23 minutes with hyperbaric oxygen (HBO) treatment at 2.5-3 absolute atmosphere[41,42].

Oxygen therapy until clinical symptoms regress or if there is no cardiopulmonary complication, until the COHb level falls below 5%; if there is a cardiopulmonary complication, it should be given until the COHb level falls below 2%. This period is usually around 4-6 hours. It has been reported that HBO therapy reduces mortality when administered in the first 6 hours. Hyperbaric oxygen therapy is more successful than normobaric oxygen therapy in the prevention of late-occurring neuropsychiatric symptoms[30].

Hyperbaric oxygen indications: the decision to treat the patient with HBO is controversial; however, treatment

is most often indicated at the scene or in hospital if unconsciousness, new neurological deficits or changes in mental status, end-organ ischemia (ECG changes), pH less than 7.1, or the patient is pregnant (especially if COHb is greater than 20%)[43]. Hyperbaric oxygen therapy is indicated if the COHb value is greater than 25%, which supports the clinical status in non-pregnant women. Hyperbaric oxygen therapy is not recommended if cardiopulmonary resuscitation is needed, if hemodynamically unstable, or if the patient has emphysema or chronic bronchitis[13,44].

Hyperbaric oxygen; it is the delivery of 100% oxygen under an absolute pressure of 2-3 atmospheres for 60 to 90 minutes. In severe cases of CO poisoning, it is administered twice daily to help repair reperfusion injury. In moderately severe cases with milder neurological deficits and symptoms, one session of treatment is sufficient. The timing of HBO is important and is most beneficial when done within the first 6 hours after exposure[45].

The severity of the poisoning; it depends on the exposure time, the CO concentration in the environment and the basic health status of the exposed person. While useful for diagnosis when detected, the first measured COHb is not a reliable way to measure severity or predict long-term outcomes[46]. The presence of neurological and cardiac symptoms indicative of tissue hypoxia, such as loss of consciousness and chest pain, is important in assessing the severity of exposure.

Ischemic injury may present with neurologic manifestations, but detection of cardiac ischemia requires ECG changes and cardiac enzyme monitoring (troponin I, CK, and CK-MB). Myocardial injury is very common, especially in those with unconsciousness or underlying vascular disease or both[47].

In supportive care; for those who are unconscious, the airway should be protected and intubation should be performed if necessary.

Serial ECG and cardiac enzyme monitoring should be performed in patients with unconsciousness, a history of cardiovascular disease, chest pain, or ECG changes.

In CO poisonings caused by smoke inhalation as a result of being in the fire, CO and cyanide poisoning should be considered and hydroxycobalamin, which is the cyanide antidote, should be applied. There is no pharmacological antidote for CO poisoning[12,42].

Prognosis

Survivors of acute CO poisoning show nearly double the long-term mortality compared with a standard population. This is more pronounced in those who are deliberately exposed than in those who are accidentally exposed[48]. Major causes of death include alcoholism, motor vehicle accidents, other accidents, and intentional self-harm, suggesting underlying neurological or psychiatric complications[23]. The quality of life of survivors is severely affected. In a study evaluating patients 51 days after poisoning, lower cognitive performance, more depression, and more post-traumatic stress disorder were found[49].

Conclusion

The prognosis of patients with CO poisoning depends on the severity of the poisoning and the clinical situation at the time of presentation. The clinical picture of CO poisoning is non-specific, although cardiac and neurological symptoms are most common. Therefore, besides cardiac and neurological diagnoses, CO poisoning should not be ignored. Treatment should be done accordingly. Treatment should be based on the diagnosis. If the symptoms are mild or moderate and there are no neurological findings, they can be discharged 4-6 hours after treatment[50]. Patients with severe intoxication should be followed up for delayed neurocognitive deficits after treatment and discharge.

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