Current treatment options for carbon monoxide-induced neurological dysfunction

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ABSTRACT

Carbon monoxide is an established dangerous toxicant with a complex mechanism of cellular toxicity. It is known to cause various neurological symptoms which can manifest both in acute as well as chronic forms. Delayed neurological deficits are often less recognizable. Radiological findings are also less specific. Hyperbaric oxygen therapy has been the mainstay of treatment over the years but is associated with its own list of complications and controversies. Current management for this important condition is discussed here.

Keywords: Carbon monoxide, hyperbaric oxygen therapy, neuroglobulin

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Carbon monoxide is a colorless, odorless and non-irritating gas produced by incomplete burning of carbon containing fossil fuels [1]. It is a leading cause of poisoning related mortality in the United States and is responsible for more than half of all the fatal poisonings occurring worldwide.

Its clinical symptoms are non specific and diverse including headache, chest pain, syncope, seizures and flu like illness. Thus, undiagnosed exposure may often lead to a significant morbidity and mortality [2, 3].

Environmental carbon monoxide exposure is usually less than 0.001% or around 10 ppm [4], but is even higher in urban areas. After cooking with a gas stove, the indoor air concentrations of carbon monoxide may reach 100 ppm [5]. Exposure to 70 ppm leads to carboxy-hemoglobin levels of 10% at equilibrium (approximately 4 hours) [2], while exposure to 350 ppm may lead to carboxy-hemoglobin levels of 40% at equilibrium [6]. Neurological manisfestations can be acute as well as chronic and depend upon the severity and duration of carbon monoxide exposure. Hypoxia is the main complication of this poisoning. Hence, oxygen therapy forms the mainstay of treatment.

Carbon Monoxide-Induced Neurological Dysfunctions

The clinical manifestations of carbon monoxide poisoning are variable and severity depends on the concentration of carbon monoxide in the inspired air, duration of exposure and general health of the involved person. The population at increased risk comprises of infants, elderly, patients with cardiovascular disorders, lung disorders, anaemia and increased basal metabolic rate [7]. The features of acute carbon monoxide poisoning are better known and more easily recognized than those having chronic exposure. Table 1 shows the clinical features manifested with the varying levels of blood carboxy-hemoglobin concentration [8]. During acute exposure, patients may complain of headache, dizziness, nausea, vomiting, emotional liability, confusion, impaired judgment, clumsiness and

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Table 1. Levels of carboxy-hemoglobin with associated clinical manifestations

Blood carboxy-hemoglobin concentration (%)	Clinical manifestations
15-20	Mild headache, fatiguability
20-30	Impaired motor dexterity, blurred vision, irritability
30-40	Severe muscle weakness, vomiting, mental confusion, delirium
40-50	Tachycardia, irritability
50-60	Seizures, respiratory insufficiency
> 60	Coma, respiratory failure, death

syncope. Prolonged exposures resulting in seizures, altered mental status or coma, may be accompanied by retinal hemorrhages and lactic acidosis [9]. Myonecrosis can also occur but it rarely leads to renal failure. Cherry-red coloured skin which is associated with severe carbon monoxide poisoning, is seen in around 2-3% of symptomatic cases [10]. Severe poisoning often leads to hypotension and sometimes pulmonary oedema with the former being the most reliable marker of prognosis.

Neuropsychiatric issues may develop insidiously over weeks to months after recovery from carbon monoxide intoxication. These include intellectual deterioration, memory impairments, cerebral, cerebellar and midbrain damage, eg. Parkinsonism and akinetic mutism with changes in personality like increased irritability, verbal aggressiveness, impulsiveness, violence and moodiness [11]. Around two fifths of patients develop memory impairments and around one third suffer late deterioration of personality [12]. Chronic carbon monoxide poisoning is often misdiagnosed as chronic fatigue syndrome or chronic infection. Carboxy-haemoglobin levels are usually not excessively elevated in these cases.

Diagnosis

History

A meticulous history should be elicited for possible ways of exposure to carbon monoxide. Patients presenting with flu like symptoms must be asked about use of wood, coal or gas based heating appliances at home or work, especially in winters. Similar symptoms in the other housemates is helpful in getting to a diagnosis.

Carboxyhemoglobin Levels

Low levels may correlate with minor symptoms such as diffuse headache or nausea whereas high levels may be fatal too. carboxy-hemoglobin levels drop rapidly after the person inhales atmospheric air (containing around 21% oxygen) as well as with time and with oxygen therapy.

Laboratory Tests

This includes complete blood counts, serum electrolytes, cardiac markers, arterial blood gas analysis (may show metabolic acidosis because of the combination of hypoxia, cellular respiration inhibition and increased metabolic demand) and serum lactate levels which have been used as a marker for severe poisoning.

Other Tests

Chest radiographs may show non cardiogenic pulmonary edema. Drug level estimation for drugs showing similar symptoms should be assessed. ECG should be done to look for arrhythmias or signs of myocardial infarction.

Neuropsychiatric Testing

This includes Mini mental state examination, Weschlar memory scale, Weschlar adult intelligence scale, or other more specific tests such as Carbon Monoxide Neuropsychological Screening Battery (CONSB) [13]. Improvement on these tests after oxygen therapy is considered as an evidence of effectiveness of the therapy.

Brain Imaging

CT scan of brain may initially show signs of cerebral edema and may later show bilateral basal ganglia hypodensities, particularly in globus pallidus and substantia nigra [14]. MRI may show diffuse white matter involvement predominantly in periventricular areas although basal ganglia, hippocampus and thalamus may also be involved. Patients may show symmetrical T2 and FLAIR hyperintensities in the globus pallidus which are often seen to resolve with time and after oxygen therapy [15]. Single Photon Emission Computed Tomography (SPECT), quantitative MRI and EEG have been used in carbon monoxide poisoning but more studies are needed to prove their specificities.

Management

After the correct diagnosis of carbon monoxide poisoning, first step should be the maintenance of airway, breathing and circulation. Patient should be advised bed rest to reduce oxygen demand and consumption.

There is no consensus currently regarding the optimal therapy of treatment in carbon monoxide poisoning for preventing acute symptoms as well as long term neurological sequelae. A bundle therapy therefore is advised which includes a combination of modalities to prevent the neurological damage [16].

Hypoxia is the most common complication of carbon monoxide poisoning. Oxygen therapy, thus is the most important measure to resolve the symptoms. Two types of oxygen therapy using 100% oxygen are used : Hyperbaric Oxygen Therapy (HBOT) and Normobaric Oxygen Therapy (NBOT). The choice of using the oxygen therapy out of these two is still controversial and lacks a robust data for either of them. The quality and results of clinical trials designed to assess the efficacy of HBOT in reducing the severity of delayed neurological symptoms have varied widely. Of several such studies, the two most important, double-blinded trials that included all patients regardless of poisoning severity came to contradictory conclusions [17, 18]. In HBOT, oxygen is at a pressure twice to thrice that of atmospheric pressure at sea level whereas it is equal to sea level atmospheric pressure in NBOT. In case of acute carbon monoxide poisoning, HBOT improves outcomes by several mechanisms. These mechanisms include acceleration of carbon monoxide elimination from hemoglobin and other heme-containing molecules, improved mitochondrial oxidative metabolism, inhibition of lipid peroxidation, inhibition of leukocyte adherence to injured microvessels and attenuation of immune-mediated delayed neurological dysfunction [19]. In addition to accelerating the rate of carbon monoxide elimination from hemoglobin, HBOT also enhances the removal of carbon monoxide from intracellular binding sites. It's timely administration prevents neuronal injury and prevents delayed neuropsychological sequelae by terminating the biological degradation [4]. If HBOT is used for delayed neuropsychiatric syndrome (DNS), the available literature suggests that benefit is greatest if treatment begins as early as possible, ideally within six hours. It is used in patients with serious intoxication showing loss of consciousness, neurological deficits, significant metabolic acidosis and carboxy-hemoglobin more than 25%. Despite its benefits, HBOT is associated with adverse effects such as cataracts, reversible myopia, tracheobronchial symptoms, self-limited seizures and barotraumas to the middle ear, the cranial sinuses or the lungs. Another limitation is that not all the hospitals are equipped with such a chamber. For patients with mild carbon monoxide poisoning (carboxy-hemoglobin level < 20%), a different regime involving 100% NBOT for 6 hours is appropriate.

Other treatment options include targeted temperature management with mild therapeutic hypothermia especially in patients with post cardiac arrest or hypoxic ischemic brain injury. Administration of sympatholytics may be useful for inhibition of the postganglionic functions of the sympathetic nervous system, thus minimizing the systemic response to acute stressor (carbon monoxide). Anti oxidants in the form of N-acetylcysteine can be used. It restores the intracellular levels of glutathione and the ability of cells to resist the reactive oxygen species. Potent anti inflammatory drugs and immune suppressant steroids such as dexamethasone or methylprednisolone could be used for severe inflammation in carbon monoxide poisoning [16].

Erythropoeitin is a glycoprotein hormone which produces red blood cells. In hypoxic states like stroke, it may be protective of neuronal cells by reducing S100B and preventing from neurological damage. In patients with carbon monoxide poisoning too, it has shown improved outcomes in management for prevention of delayed neurological sequelae [20]. Other drugs such as ziprasidone and donepezil have been used but lack data to support their use.

Latest studies suggest the introduction of a potential treatment for carbon monoxide poisoning based on near irreversible binding of carbon monoxide by an engineered neuroglobin (Ngb) with a mutated distal histidine (H64Q). Ngb is a six-coordinate hemoprotein, with the heme iron coordinated by two histidine residues. Mutation of distal histidine to glutamine (H64Q) and substitution of three surface cysteines with less reactive amino acids forms a five-coordinate heme protein (Ngb-H64Q-CCC). This molecule exhibits an unusually high affinity for gaseous ligands, with a P50 (partial pressure of O2 at which hemoglobin is half-saturated) value for oxygen of 0.015 mmHg. Ngb-H64Q-CCC binds about 500 times more strongly than does hemoglobin. Incubation of Ngb-H64Q-CCC with 100% carbon monoxide-saturated hemoglobin, either cell-free or encapsulated in human red blood cells, reduces the half-life of carboxyhemoglobin to 0.11 and 0.41 min, respectively, from ≥ 200 min when the hemoglobin or red blood cells are exposed only to air. Infusion of Ngb-H64Q-CCC to carbon monoxide-poisoned mice enhanced carbon monoxide removal from red blood cells, restored heart rate and blood pressure, increased survival, and was followed by rapid renal elimination of carbon monoxide-bound Ngb-H64Q-CCC. Heme-based scavenger molecules with very high carbon monoxide binding affinity, such as this mutant five-coordinate Ngb, are potential antidotes for carbon monoxide poisoning by virtue of their ability to bind and eliminate carbon monoxide [21].

Also, carbon monoxide can be photodissociated and recombinated to wild type (WT) and H64Q Ngb. The distribution of carbon monoxide within the proteins differs substantially due to rearrangement of amino acids surrounding the distal heme pocket leading to the decrease of the distal pocket volume in H64Q Ngb in comparison to WT Ngb, trapping migrating carbon monoxide molecules in the distal pocket. This shows that the mutation implicates the shortening of the time scale of carbon monoxide geminate recombination, making H64Q Ngb 2.7 times more frequent binder than WT Ngb [22]. However, more studies are needed for the substantiation of this novel, yet promising therapy option.

Patients with carbon monoxide poisoning should be followed up periodically after discharge. The rate and extent of recovery after poisoning are variable, and recovery is complicated by the development of sequelae, which can persist after exposure or develop weeks after poisoning [4] and which can be permanent. Specific therapy for sequelae is not available. Such patients should have their symptoms treated, through psychiatric, vocational, cognitive, speech, occupational, and physical rehabilitation, although data on the effects of these interventions in patients with carbon monoxide related sequelae are lacking.

Prevention

During winters, carbon monoxide poisoning should be suspected in all patients presenting with flu-like symptoms (e.g., headache, nausea, dizziness),and with a doubtful history. Proper public education on the safe operation of heaters, appliances, fireplaces and internal combustion engines is necessary. Burn victims, with an evidence of smoke inhalation from enclosed fire, should undergo testing for carboxy-hemoglobin levels. Carbon monoxide detectors with alarms can also improve home and workplace safety [8].

CONCLUSION

There is currently no optimal treatment for carbon monoxide poisoning and its delayed neurological sequelae. Carboxy-hemoglobin has poorer correlates with severity of carbon monoxide poisoning. HBOT, which is a well known and widely used modality, has become controversial and it is unlikely that it will hold its place as the sole standard optimal treatment in future. So, in patient management, there is a need for new markers in monitoring and evaluation. A bundle therapy with targeted temperature management is the ideal way of management. Further research is necessary for novel agents which act depending on the underlying pathophysiological process of causation of delayed neurological sequelae.

Conflict of interest

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