CORTEX XXX (2015) 1–8

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Special issue: Historical paper

The neurotoxicology of carbon monoxide – Historical perspective and review

Oliver T. Sykes [a,*] and Edward Walker [b]

[a] Department of Anaesthesia, Royal National Throat, Nose and Ear Hospital, University College London Hospitals NHS Foundation Trust, London, UK

[b] Department of Emergency Medicine, Mid-Yorkshire Hospitals NHS Trust, Wakefield, UK

ARTICLE INFO

Article history:
Received 20 March 2015
Reviewed 21 May 2015
Revised 16 July 2015
Accepted 23 July 2015
Published online xxx

Keywords:
Carbon monoxide
Carboxyhaemoglobin
Neuropsychiatric impairment

ABSTRACT

Carbon monoxide (CO) has been recognized as a poison for centuries, and remains one of the most common causes of both accidental and deliberate poisoning worldwide. Despite this, there are widespread misconceptions with regards to the mechanisms, diagnosis and outcomes of CO induced poisoning such as the idea that CO poisoning is rare; that carboxyhaemoglobin levels above 20% and loss of consciousness are required before nervous system damage ensues; and that the binding of CO to haemoglobin is the only mechanism of toxicity. Prevention and diagnosis of CO poisoning is hampered by the lack of awareness of CO as a cause of illness, among both the general public and healthcare professionals. To complicate matters further there is no standardized definition of CO poisoning. Carboxyhaemoglobin levels are often used as a marker of CO poisoning, yet plasma levels rapidly reduce upon removal of the source and are therefore an unreliable biomarker of exposure and tissue damage. Adverse neuropsychiatric outcomes after CO poisoning are difficult to define, especially as they fluctuate, mimic other non-specific complaints, and are not present in all survivors. This paper challenges a number of misconceptions about CO poisoning which can result in misdiagnosis, and consequently in mismanagement. We illustrate how recent developments in the understanding of CO toxicology explain the particular susceptibility of the central nervous system to the effects of CO exposure.

1. Introduction

Carbon monoxide (CO) is a naturally occurring gas that has been present on this planet since its formation and might reasonably be regarded as one of our oldest toxicological adversaries. Aristotle (384–322 BC) first recorded that burning coals released toxic fumes, and it is further recorded in the 3rd century BC that Hannibal employed it to kill prisoners. It is also believed that CO released from burning coal poisoned two Byzantine emperors (Lascaratos & Marketos, 1998). More recently both the Soviets and the Nazis used CO poisoning in gas vans in the 1930s, during the 'Great Purge' and during the early years of the extermination program (Merridale, 2001).

* Corresponding author.
E-mail address: o.sykes@nhs.net (O.T. Sykes).

http://dx.doi.org/10.1016/j.cortex.2015.07.033
0010-9452/

2. Properties and sources of CO

CO is a colourless, odourless, and non-irritant gas, which mixes evenly with room air and has no acidic or basic properties. It is a product of incomplete combustion of carbonaceous matter and is undetectable by human smell, taste or sight. Common sources in the developed world include improperly installed or poorly maintained cooking and heating appliances, especially in caravans and tents, and the exhaust of all internal combustion engines such as motor vehicles, generators, lawn mowers and power tools, especially when used near or within closed spaces (Wu & Wang, 2005). Even small gasoline-powered engines are capable of producing toxic levels of CO (Earnest, Mickelsen et al., 1997).

Case reports have identified more unusual sources, including soda lime used in anaesthetic breathing circuits, leakage from neighbouring properties, outdoor proximity to marine engines accompanied by unfavorable wind conditions, the smoking of 'hookah' pipes, methylene chloride exposure (Fagin, Bradley, & Williams, 1980) and most recently the air space above stored (unburned) pelleted wood fuel (Gauthier et al., 2012). Cigarette smoke may contribute to CO exposure (Cox & Whichelow, 1985) and to measurable carboxyhaemoglobin (COHb) levels indoors (Shaper et al., 1981), although other authors have found that 'second hand' tobacco smoke may be less harmful in terms of CO poisoning by proxy. The highest reported CO levels are observed in garages with internal combustion engines and when cooking indoors on open fires. Catalytic converters in modern cars reduce CO levels in engine exhaust fumes considerably, but fatal accidental poisonings and successful suicides still occur. With reduced CO emissions in vehicle exhaust, simple hypoxic asphyxia, with normal carboxyhaemoglobin levels, is also sometimes found.

3. Features of poisoning

CO poisoning may be acute (exposure up to 24 h), chronic (exposure longer than 24 h, including intermittent exposure), or acute-on-chronic. A not uncommon scenario encountered by physicians might be a near-fatal episode of exposure which attracts the attention of emergency services. Once a full history is obtained, a background of many months of chronic, misdiagnosed ill health often emerges. Neuropsychiatric sequelae are a constellation of signs and symptoms that are commonly reported with poisoning (Table 1), and may be immediately apparent, or preceded by a period of apparent full recovery. The latter picture describes the phenomenon known as delayed neuropsychiatric sequelae.

The severity of poisoning depends upon both environmental and human factors such as the relative concentration of the gas in air, ambient ventilation, atmospheric pressure, pre-existing cerebral or cardiovascular disease, metabolic rate, duration of exposure and pulmonary function. The very young, the very old, and the unborn are particularly susceptible to the effects of CO. The long-term effects on those who survive their exposure remain unclear. Some risk factors for unfavourable outcomes are recognized, such as the subject's age and the duration of exposure, but others are as yet unknown.

There is therefore a wider range of non-specific symptoms that can be temporary or persistent (Table 1), which make diagnosis difficult, and treatment and the defining of outcome measures challenging. Correlations of severity of symptoms with higher blood levels of COHb have been made, however these correlations do not predict outcome.

Significant poisoning can occur in the absence of raised carboxyhaemoglobin

COHb levels fall quickly after a subject's removal from the source, and are likely to have dropped significantly by the time testing is carried out. For example, Zavorsky et al. found an elimination half-life for CO of between 50 and 70 min on 100% oxygen in 2014 (Zavorsky et al., 2014), which is similar to that found for COHb by Weaver et al. of 74 ± 25 min in 2000 (Weaver, Howe, Hopkins, & Chan, 2000). COHb levels are traditionally used to determine the 'severity' of exposure, but not only are those levels notoriously difficult to interpret given the short half-life described, but severity of outcome in terms of both acute and lasting symptoms have been shown to bear little relationship to the severity of exposure, however measured (Chambers, Hopkins, Weaver, & Key, 2008).

CO has an affinity for human haemoglobin about 240 times greater than that of oxygen (Rodkey, O'Neal, Collison, & Uddin, 1974), depending on pH and temperature. However extrapolation backwards to estimate peak levels may miss significant

Table 1 – Signs and symptoms of acute or chronic CO poisoning.

Symptoms:
Headache, dizziness, nausea, vomiting, irritability, weakness, fatigue, syncope, angina, 'flu-like' symptoms.
Depression, anxiety, irritability, recurrent infections and hair changes are reported more commonly in 'chronic' exposures.
Signs:
Ataxia, agitation, impairment of consciousness, respiratory failure, tachycardia, tachypnoea, hypotension, myocardial ischaemia and infarction, ST depression, prolonged QT interval, atrial fibrillation, pneumonia, high blood sugar, lactic acidosis, Cerebral edema and metabolic acidosis develop in serious cases.
Less common features:
Skin blisters, rhabdomyolysis, acute renal failure, pulmonary oedema, retinal haemorrhages, cortical blindness, choreoathetosis and mutism.
Neuropsychiatric features:
Memory loss, depression, anxiety, disorientation, apathy, mutism, irritability, inability to concentrate, personality change, Parkinsonism, including urinary and/or faecal incontinence, gait disturbance, dementia, psychosis, hallucinations, seizures, coma and death.
Fluctuating signs and symptoms are the rule

Please cite this article in press as: Sykes, O. T., & Walker, E., The neurotoxicology of carbon monoxide – Historical perspective and review, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.07.033