REVIEW

Chronic and occult carbon monoxide poisoning: we don't know what we're missing

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Carbon monoxide is colourless, odourless, and ubiquitous in our environment. In large concentrations it is known to be a stealth killer. This article reviews the evidence that carbon monoxide is a public health menace even in much lower concentrations.

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The purpose of this review is to examine the literature regarding occult and chronic exposure to low levels of carbon monoxide (CO)—that is, levels insufficient to cause emergency department attendance or admission to hospital *with a clinical diagnosis* of acute CO poisoning, although this in fact is the cause of the symptoms.

More is known about acute CO poisoning, but knowledge and awareness of chronic poisoning is progressing slowly. There is a strong possibility that low level exposure to CO is responsible for widespread and significant morbidity, however the clinical syndrome produced is often overlooked because of a range of presentations, obscure symptoms, and a lack of awareness of the problem.[1]

In the USA, comparatively small changes in ambient levels of CO as a result of pollution have been shown to affect rates of presentation to emergency departments with various complaints.[2–4] This raises the possibility that large numbers of patients may be seen in UK emergency departments with symptoms caused by, or disease states worsened by, exposure to CO without staff being aware of the fact.[5] There also exists the issue of acute poisoning from domestic gas appliances and other sources, which result in symptoms, and illness not recognised by medical staff.[6–8] This issue also falls into the remit of this review as cases of "occult poisoning" (see box 1 for definitions of CO poisoning).

CARBON MONOXIDE POISONING

The hidden poison

CO is a colourless, odourless, non-irritant gas. It is present in our environment naturally (40%), and artificially as a result of human activities (60%). Vast amounts of CO are released into the atmosphere by burning fossil fuels (forest fires, car exhaust emissions, and burning natural gas).[9] People may be chronically exposed to CO as a result of smoking or from the atmosphere. In addition, endogenous CO is also produced as a result of the breakdown of haem.[10]

There are many other potential sources of CO, often recorded in case reports of poisoning (table 1). These sources are frequently associated with confined spaces. They include incomplete combustion and inadequate ventilation of domestic natural gas, indoor burning of charcoal for barbecues, propane gas cylinders (forklift trucks), petrol powered generators, and methylene chloride exposure from spray paint (hepatic conversion to CO).[11–15]

Why can carbon monoxide poisoning be missed?

The medical literature is littered with dozens of case reports and review articles related to the

Box 1 Definition of acute, chronic, and occult carbon monoxide poisoning

In the context of this article:

- "*Acute CO poisoning*" is used to indicate those cases of poisoning that have come to the attention of medical practitioners immediately after exposure. This usually occurs after a single, large exposure to the gas, and may involve one or more people. Most of our current medical and scientific knowledge is based on acute poisoning.
- "*Chronic CO poisoning*" is used to indicate those cases when patients are exposed on more than one occasion to the gas—usually at comparatively low concentrations. These patients will develop symptoms related to exposure to the toxin, if concentrations and duration of exposure are great enough. After repeated exposure, the problem may come to the attention of medical practitioners.
- "*Occult CO poisoning*" is used to indicate those cases of CO poisoning that may never come to the attention of a medical practitioner. In most cases, this is as a result of chronic CO poisoning and most frequently the patient will not even ask for a medical opinion. Occasionally acute poisoning as a result of exposure to high concentrations of gas may remain occult, and although the patient presents to a medical practitioner—the diagnosis is missed (at least until the patient re-attends, often with cohabitees with similar symptoms). Occasionally, deaths have occurred.
- Pyramid of disease: CO poisoning can be looked upon as a "disease" with a pyramid of presentation—the tip of the iceberg is overt acute poisoning, while the base is occult, low level exposure. A difficult question to answer is: how big is the base? Even ambient levels of CO in the atmosphere as a result of pollution cause changes in the hospitalisation and mortality rates of patients with certain diseases.

Abbreviations: CO, carbon monoxide; COHB, carboxyhaemoglobin

Box 2 Common symptoms caused by carbon monoxide poisoning

- Headache
- Dizziness
- Weakness
- Vomiting and diarrhoea
- Loss of consciousness (without lateralising signs)
- Seizure
- Confusion
- Angina
- Breathlessness

insidious nature of this poison. Editorials urge doctors to be forever vigilant in the search for victims of CO, yet the diagnosis continues to be missed, not infrequently. Why is this?

(1) The diagnosis is made sufficiently rarely for doctors to forget about it. Even when faced with classic symptoms (box 2) and signs, there is a long list of differential diagnoses.

(2) To make the diagnosis, a blood test with access to a co-oximeter, to measure carboxyhaemoglobin (COHB) levels is required: that in itself may be enough to dissuade some clinicians. Many still believe that an arterial sample is required whereas a venous sample is sufficient.[16]

(3) At the part of the spectrum dealing with low levels of CO exposure there is confusion as to what constitutes poisoning. There are several reasons for this:

- We all have some COHB in our blood as a result of endogenous production of CO.[10]
- Atmospheric pollution can increase levels of COHB by a small amount in non-smokers.[17 18]
- Smokers increase COHB levels to between 5% and 9%, but heavy smokers can have levels up to 15%.[18 19] In the indoor environment, smokers become net contributors to ambient CO levels.
- There is poor correlation between COHB levels and symptoms anyway, especially in smokers at low atmospheric levels of CO.[12]
- A biochemical marker for chronic CO poisoning has yet to be found.
- There has been a relative paucity of research into the problem.
- There is still debate about the mechanism of CO toxicity.[20]
- It has been argued that measuring low levels of COHB accurately will require gas chromatography for accuracy. Gas chromatography is relatively expensive and inaccessible.[9]
- The kinetics of CO uptake and excretion are complex, even in controlled scientific environments, with the time to reach a steady state of COHB in the blood known to be greater than eight hours at rest.[21] Exercise decreases the time to reach steady state and breathing higher concentrations of CO produces a higher concentration of COHB at equilibrium.[22] COHB decreases with a half life of approximately 320 minutes in air. However this half life is further decreased to 80 minutes if 100% oxygen is given to the patient.[23] In the everyday situation with patients possibly smoking (or non-smokers breathing atmospheric pollution), and entering then leaving potential sources of CO at random, one can only guess at the actual kinetics in that person, especially if they have received oxygen en route to the hospital.

The net effect of the list mentioned above is to leave the clinician (who has thought of a possible diagnosis of CO poisoning) with the difficult question: "Is the level of COHB in this person sufficient to be causing their clinical condition, and if so, is the exposure to CO acute or chronic and what relevance does their smoking history have?"

WHAT IS THE CURRENT EVIDENCE THAT CO IS AN OCCULT POISON?

Descriptive patient studies into chronic/occult poisoning

Balzan *et al* measured COHB levels in 104 patients admitted to a coronary care unit.[24] Three patients had definite CO poisoning and a further five had evidence of minor exposure. In a later study, Balzan *et al* screened 307 acute neurological admissions.[25] Three patients had CO poisoning (from a group of 29 patients with impaired consciousness and no lateralising signs).

In a similar study, Heckerling *et al* screened 168 consecutive acute neurological admissions and found five cases of CO intoxication, two of which were from a group of 43 patients admitted for epileptic seizures.[26] They also investigated those patients presenting with headache. Of a total of 140 patients presenting with headache, 48 had COHB levels measured. Seven had increased levels of CO (greater than 10%), giving a prevalence of CO toxicity in the study of 14.6%. Three of the seven with CO poisoning complained of headaches for more than one week and three were non-smokers. All seven were found on follow up to have reasons other than smoking for their increased CO levels.[27] The same group carried out another study 12 months later and discovered COHB levels greater than 10% in four of 146 patients (3%) with headache. Of the study population, 89 were contacted for completion of risk factor data. Significant predictors of increased COHB levels were number of cigarettes smoked daily, use of stoves for heat, and concurrently symptomatic cohabitants.[28] The following year they attempted to use these predictors to validate a

Table 1 Common causes of accidental CO poisoning

Cause	Reason	Prevention
Water heater, furnace	Clogged burner, blocked vent, faulty pilot light, damage from basement flooding	Regular maintenance and repairs, correct installation, look for yellow flames
Fireplace, chimney	Poor ventilation because of birds' nests, soot, leaves	Regular check and sweep of chimney, chimney cap
Portable heater	All combustion products are vented into room	Keep well maintained. Do not allow build up of rust, dirt, etc. Never use in enclosed space. Some devices have CO shutoff devices.
Kitchen range/stove	Rust, clogged burner, dirt, improper installation, faulty device	Regular maintenance and repairs, correct installation, look for yellow flames, never warm home using a natural gas or propane oven
Attached garage	Running car engine in an attached garage, especially if door closed	Never warm up car engine in garage
Lawnmowers, leaf/snowblowers, fork-lift trucks,	Petrol or propane driven engines use in confined spaces	Awareness of the risk of using such devices in enclosed spaces, Health and Safety legislation
Indoor charcoal barbeques	Release of CO from charcoal embers	Never use charcoal barbeques indoors
SCUBA compressors	CO exhaust from compressor too close to air intake	Use only authorised agencies to fill tanks

predictor model for identifying CO poisoning in patients attending the emergency department. However, the model only identified three of the four patients with a COHB level greater than 10% (from a total of 61 patients tested).[29] In what seems to be the final publication in the series, they carried out a more general screening investigation of 753 acute surgical, medical, neurological, and psychiatric admissions and only two minor cases of intoxication were identified.[30] This suggests that widespread screening in the emergency department would be expensive and unproductive unless the screening tool was quick and cheap to use.

Dolan *et al* investigated patients presenting to the emergency department with flu-like symptoms. Fifty five patients with eligible symptoms had COHB levels measured. Thirteen patients (23.6%) had COHB levels greater than 10%. However, a total of 637 patients had symptoms that would have allowed inclusion in the study (from a total of 3998 seen in the study period) and we need to ask if there was there some sort of bias involved in excluding so many patients.[31]

An indication of symptom incidence suffered by CO poisoned people is obtained in a study by Burney, which described mass poisoning in a high school.[12] A total of 184 people were exposed to 500 ppm for 150 minutes before staff were alerted (COHB levels were up to 30% in those tested). The three most commonly reported symptoms were headache (90%), dizziness (82%), and weakness (53%). Smokers had the same time of onset of symptoms as non-smokers once toxic levels approached. However they felt "back to normal" earlier than did non-smokers despite the same rate of elimination of CO suggesting, to quote the authors: "Smokers have more tolerance for low levels of CO than do non-smokers".

The symptoms associated with CO poisoning, such as headache, weakness, dizziness, and poor exercise tolerance are frequently encountered by general practitioners, and not infrequently encountered in emergency departments. How many of those patients who have chronic CO poisoning and present with such symptoms are correctly diagnosed? This is a very difficult question, and one that is yet to be answered. There is evidence that some, at least, are missed—Webb and Vaitkevicius published a case report of a 73 year old woman who was investigated over a four month period for a variety of neurological symptoms before the correct diagnosis was made,[32] and Myers *et al* described eight case histories of chronic CO exposure, the duration of which were from three weeks to three years.[1]

Population studies

In 1969, Cohen *et al* published a paper demonstrating an association between increased mortality attributable to myocardial infarction and periods of increased ambient levels of pollution with carbon monoxide in Los Angeles.[33] Kurt *et al* then looked at the frequency of acute cardiorespiratory complaints with regard to ambient levels of CO.[3] They found a low level, but statistically significant, association between acute cardiorespiratory illness and ambient CO levels. The problem with population studies is that of ecological fallacy, in which certain trends that are seen are not necessarily as a result of the factor being studied.[34] A good example in this case would be other pollutants rather than CO causing the symptoms. However, Kurt *et al* found no association between ambient levels of other atmospheric pollutants and cardiorespiratory illness.

In a study involving seven large US cities, ambient CO levels were associated with hospital admissions for congestive cardiac failure with a relative risk for admission ranging from 1.1 to 1.37 when associated with an increase of 10ppm CO concentration.[35] Cobb and Etzel looked at all unintentional CO related deaths in the USA from 1979 to 1988.[36] The number of unintentional deaths decreased year on year from 1513 in 1979 to 878 in 1988, mainly, the authors thought, as a result of a more than 90% decrease in exhaust CO emissions in new cars since 1968. These deaths of course are attributable to acute poisoning. However, the authors go on to comment that the actual number of CO related deaths may be much higher than they reported, because the levels of CO commonly found in urban outdoor air may induce arrhythmia, angina, and sudden death in people with heart disease.[37] They suggest that "small changes in ambient levels [of CO] may cause substantial changes in the rate of cardiac arrest among susceptible individuals" and make the comment that the rate of death attributable to coronary heart disease in the USA began decreasing in 1968, at the same time that total CO production dropped by 30% in response to the Clean Air Act.

In the UK almost seven million tonnes of CO are emitted into the atmosphere each year, 87% of this is from petrol engines.[38] This represents a 50% increase from the 1970 values, in line with increasing traffic volume. However, since 1990 there has been a decline in vehicle emissions, probably because of an increased use of catalytic converters on cars. The Expert Panel on Air Quality Standards (EPAQS) was set up by the UK Secretary of State for the Environment in 1991. This panel advises on air quality standards, taking account of best evidence regarding the effects of pollutants on human health. They recommend a Department of the Environment, Transport and the Regions (DETR) Air Quality Standard of 10ppm CO, measured as a running eight hour average. The reasoning behind this is that this level of exposure will keep COHB levels in non-smokers below 2.5%, a level below that at which patients with angina are known to become symptomatic. Regular smokers are unlikely to be affected by such conditions alone, as their COHB levels are already higher than can be reached by breathing this air. EPAQS standards are occasionally exceeded—but only rarely, for example in eight UK cities in the whole of 1992 there was a mean number of less than one day per city when the recommended standard was exceeded.[38] It would follow from this, that ambient levels of CO in the atmosphere probably have little or no effect on the UK population—except perhaps on rare occasions. Unfortunately things do not seem to be this simple. There is evidence, again from the USA, that levels at or below 10ppm CO still have an effect on rates of hospitalisation for cardiovascular problems[39] and congestive heart failure.[40] There are three possible reasons for this[40]:

- Firstly, levels at ambient monitors poorly reflect individual exposures. It is better to think of increased levels (but still apparently relatively low) at monitor stations representing a greater probability of individual exposure to increased levels, exceeding EPAQS standards.
- Secondly, people with heart disease (especially congestive heart failure) may be uniquely susceptible to CO.
- Thirdly, the presence of additional stressors, such as low temperatures may modify the effect of CO.

One thing seems certain—there is a need for independent, UK based research into the effect of ambient levels of CO, no matter how low, on hospitalisation and mortality rates.

Patient group studies

At levels of COHB greater than 10% patients with pre-existing cardiac disease experience increased severity and duration of angina and if levels rise above 15% they are at increased risk of myocardial infarction. If a patient *has* had an acute myocardial infarction, the threshold for ventricular fibrillation can be reduced to 9% COHB.[41] Patients with severe chronic bronchitis or emphysema experience a significant reduction in the walking distance when breathing air after exposure to CO[42] and intermittent claudication occurs with less provocation in patients with low levels of COHB.[41] Even in normal subjects a COHB concentration as little as 4.4% has been shown to limit work capacity and maximal oxygen consumption.[43]

THE ATHEROGENIC POTENTIAL OF CO

Some people have suggested that CO itself can produce atheroma. However, Smith and Steichen reviewed all the available epidemiological and animal studies in 1993. They reviewed a total of 41 studies and their conclusion was that CO is not atherogenic.[44]

DELAYED NEUROPSYCHIATRIC SYNDROME

In patients with acute poisoning, 30% or more may experience delayed onset of neuropsychiatric symptoms.[45] Symptoms include cognitive and personality changes, dementia, psychosis, parkinsonism, amnesia, depression, and incontinence. There is also good evidence that apparently minor low level acute and chronic exposure causes varying degrees of neuropsychological impairment.[1 46] It is postulated that CO causes lipid peroxidation of neurological tissues.[47] Early hyperbaric oxygen therapy decreases the extent of lipid peroxidation and this would explain the decreased incidence of neuropsychiatric sequelae after hyperbaric treatment. The regions of the brain most frequently involved include the globus pallidus and deep white matter.[48]

A neuropsychological screening battery (CONSB) to assess CO neurotoxicity has been devised,[49] but this has no practical use in predicting cases of poisoning in the emergency department setting.

DOMESTIC CO DETECTORS

A wide variety of domestic CO detectors are currently on the market.[50] There are three main types:

Biomimetic (Chem-Optical, Gell Cell technology)

These sensors attempt to mimic chemically the effect that CO has on haemoglobin. A gel coated disc will change colour and darken in the presence of CO. A sensor then recognises the colour changes and sets of an audible alarm. Such detectors are inexpensive, and require very little electricity and therefore can be battery powered. They do not alarm incorrectly in the presence of common household gases, but high and low temperature or humidity can trip the alarm. Low levels of CO can be detected, but a problem with some of these devices is the sensor's low reset capability. It can take up to 48 hours for the sensor to reset and during this time, cumulative readings may trigger a false alarm.

Metal oxide semiconductor

These are the oldest of the domestic sensor devices, and millions have been manufactured and sold. Heated tin dioxide reacts with CO. Because the tin needs to be repeatedly heated, a lot of energy is required and therefore these detectors are plug in devices, using mains electricity. An advantage is that batteries do not need to be checked. The detectors respond quickly to rising levels of CO. False alarms are, however, quite common because of cross sensitivity with other household gases. With time there may be loss of sensitivity to CO and calibration drift. Metal oxide semiconductor devices are unable to detect levels of CO below 100 ppm and are therefore no good for detecting low level, chronic exposure.

Electrochemical

Electrochemical devices have been used in industrial detectors for 20 years. They are being used with increasing frequency in domestic detectors. Three platinum electrodes are immersed in electrolyte solution and reaction with CO induces a small electric current. The devices are battery powered or have built in power supplies, and have audible alarms and LCD displays with a memory feature. These detectors can detect low levels of CO and are very accurate initially. They tend to be expensive and with time are susceptible to contamination and calibration drift. Electromagnetic radiation may trigger false alarms. A major disadvantage is that the life span of the devices can be as little as two years.

Many detector devices on the market have created significant false alarm problems as well as life threatening failures to go off when dangerous levels of CO are present. Manufacturers and government agencies throughout the world are still trying to develop the ideal device, which will have increased resistance to false alarms and false negatives, improved accuracy, and increased alarm reliability and repeatability. There is no doubt however, that lives will continue to be lost, and there will be large numbers of people chronically exposed to low levels of CO unless there is a dramatic increase in the number of CO detectors installed into UK homes.

EXPIRED BREATH CARBON MONOXIDE METERS

Simple and cheap expired breath CO measuring devices are now available (for example, piCO and ToxCO smokerlyzers, Bedfont Scientific Ltd, Rochester, Kent, UK). These devices are easily calibrated and take a matter of seconds to use. Although still predominantly used by general practitioners to assess smokers trying to give up the habit, they are excellent tools for CO poisoning diagnosis in the emergency department. The instruments are compact and portable, and have been validated.[51 52]

SUMMARY

There is sufficient evidence available to suggest that significant numbers of our population are being poisoned by low concentrations of CO. In otherwise healthy people, occult indoor exposure may result in commonplace symptoms such as headache, dizziness, weakness, and difficulty in concentrating. In people with pre-existing disease, pollution alone may result in increased morbidity and mortality—even in non-smokers who are exposed to ambient levels of CO below the EPAQS standard of 10 ppm as an eight hour average. Constant monitoring will be required to ensure current EPAQS standards are not exceeded in the future, and independent public heath research is required to see if the standard should be lowered.

At the moment the best way of identifying victims of CO poisoning seems to be vigilance and awareness in medical practitioners. Neuropsychological tests (for example, CONSB) have been shown to be useful in neurological assessment of recognised poisoning,[1] however it seems unlikely that these will develop into a commonplace diagnostic tool in the emergency department setting. There still remains the need to identify a biochemical marker for chronic CO poisoning, but research has recently shown that CO is also a physiological messenger similar to nitric oxide.[9] This has resulted in increased interest in CO at the biochemical level and hopefully one of the results of this research will be the identification of such a marker.

So what is the take home message for busy emergency department staff? Consultants and managers should encourage the use of domestic CO alarms as a "blanket cover" of the population at large. It should be possible to incorporate the use of a smokerlyzer into the triage process although the efficiency of this extra step would need to be assessed. The ideal triage device would be based on the same principles as the oximeter. Instead of measuring the intensity of absorption at two different wavelengths of light to indicate the relative amounts of oxyhaemoglobin and deoxyhaemoglobin, the device would have to account for the extra dimension of carboxyhaemoglobin. In effect, it would be a portable "carboximeter" placed over the finger. At the moment, such a device is not commercially available.

Otherwise, in the current situation doctors and triage nurses will need to be aware that patients with low level CO poisoning could be attending the department on a regular basis. Certain symptoms and clinical situations should serve as a trigger alert for further inquiry (a classic example would be a previously healthy student living in rented accommodation who recently developed headaches, coinciding with the onset of winter). If an expired breath detector is not available, the simplest investigation of choice is a venous sample to measure COHB concentration. In the situation where the COHB level is within the accepted normal range, but chronic CO poisoning is still strongly suspected, the patient should be encouraged to have any domestic gas appliances checked as a matter of urgency.

There is a grey mist shrouding the whole subject of CO poisoning epidemiology. There isn't yet a reliable screening blood test available, as there is for example in the diagnosis of diabetes, or hypothyroidism. Until there is such a simple investigation we will not know what we're missing.

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