Exhibit 3

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MARTINSVILLE VIRGINIA CIRCUIT COURT CASE NO. CR19000009-00

UNITED STATES DISTRICT COURT CASE NO. 1:13-CR-435-1
MIDDLE DISTRICT OF NORTH CAROLINA

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Carbon monoxide poisoning (acute)

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CS and KO declare that they have no competing interests.

Abstract

Introduction

Carbon monoxide is an odourless, colourless gas, and poisoning causes hypoxia, cell damage, and death. Exposure to carbon monoxide is measured either directly from blood samples and expressed as a percentage of carboxyhaemoglobin, or indirectly using the carbon monoxide in expired breath. Carboxyhaemoglobin percentage is the most frequently used biomarker of carbon monoxide exposure. Although the diagnosis of carbon monoxide poisoning can be confirmed by detecting elevated levels of carboxyhaemoglobin in the blood, the presence of clinical signs and symptoms after known exposure to carbon monoxide should not be ignored.

Methods and outcomes

We conducted a systematic review and aimed to answer the following clinical question: What are the effects of oxygen treatments for acute carbon monoxide poisoning? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2007 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

Results

We found 12 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions.

Conclusions

In this systematic review, we present information relating to the effectiveness and safety of the following interventions: 100% hyperbaric oxygen, oxygen 28%, and oxygen 100% by non-re-breather mask.

Key Points

The main symptoms of carbon monoxide poisoning are non-specific in nature and relate to effects on the brain and heart. The symptoms correlate poorly with serum carboxyhaemoglobin levels.

- People with comorbidity, the elderly or very young, and pregnant women are most susceptible.
- Carbon monoxide is produced by the incomplete combustion of carbon fuels, including inadequately ventilated heaters and car exhausts, or from chemicals such as methylene chloride paint stripper.
- Poisoning is considered to have occurred at carboxyhaemoglobin levels of over 10%, and severe poisoning is associated with levels over 20-25%, plus symptoms of severe cerebral or cardiac ischaemia. However, people living in areas of pollution may have levels of 5%, and heavy smokers can tolerate levels up to 15%.
- Severe poisoning can be fatal, and up to a third of survivors have delayed neurological sequelae.

Immediate care requires removal of the person from the source of carbon monoxide and giving oxygen through a non-re-breather mask.

- Normobaric 100% oxygen reduces the half-life of carboxyhaemoglobin and is considered to be effective, but studies proving benefit compared with air or lower concentrations of oxygen have not been identified, and would be unethical.
- Paramedics use28% oxygen and is thought to be beneficial compared with air, but may be less effective than higher concentrations.
- We don't know what is the optimum duration of oxygen treatment, but it is usually continued for at least 6 hours, or until carboxyhaemoglobin levels fall below 5%.

We don't know whether hyperbaric oxygen is more effective than normobaric 100% oxygen at preventing neurological complications in people with mild-to-moderate or moderate-to-severe carbon monoxide poisoning.

- Clinical benefit of hyperbaric 100% oxygen may depend on the treatment regimen used.
- The possible benefits of hyperbaric oxygen for an individual need to be weighed against the hazards of a long journey by ambulance.

About this condition

Definition

Carbon monoxide is an odourless, colourless gas, and poisoning causes hypoxia, cell damage, and death. **Diagnosis of carbon monoxide poisoning:** Exposure to carbon monoxide is measured either directly from blood samples and expressed as a percentage of carboxyhaemoglobin, or indirectly using the carbon monoxide in expired breath. Carboxyhaemoglobin percentage is the most frequently used biomarker of carbon monoxide exposure. Although the diagnosis of carbon monoxide poisoning can be confirmed by detecting elevated levels of carboxyhaemoglobin in the blood, the presence of clinical signs and symptoms after known exposure to carbon monoxide should not be ignored. The signs and symptoms of carbon monoxide poisoning are mainly associated with the brain and heart, which are most sensitive to hypoxia. The symptoms of carbon monoxide poisoning are non-specific and varied, and include headache, fatigue, malaise, "trouble thinking", confusion, nausea, dizziness, visual disturbances, chest pain, shortness of breath, loss of consciousness, and seizures. In people suffering

from co-morbidities, symptoms such as shortness of breath or chest pain may be more evident. The classical signs of carbon monoxide poisoning — described as cherry-red lips, peripheral cyanosis, and retinal haemorrhages — are rarely seen. **Interpretation of carboxyhaemoglobin levels:** Non-smokers living away from urban areas have carboxyhaemoglobin levels of 0.4-1.0%, reflecting endogenous carbon monoxide production, whereas levels of up to 5% may be considered normal in a busy urban or industrial setting. Smokers are exposed to increased levels of carbon monoxide in cigarettes, and otherwise healthy heavy smokers can tolerate levels of carboxyhaemoglobin of up 15%. The use of carboxyhaemoglobin percentage as a measure of severity of carbon monoxide poisoning, or to predict treatment options, is limited because carboxyhaemoglobin levels are affected by removal from the source of carbon monoxide and any oxygen treatment given before measurement of percentage carboxyhaemoglobin. Additionally, people with co-morbidities that make them more sensitive to the hypoxia associated with carbon monoxide can present with symptoms of poisoning at carboxyhaemoglobin levels that are either low or within the normal range. Attempts have been made in the literature to equate symptoms and signs to different carboxyhaemoglobin levels, but it is accepted that carboxyhaemoglobin levels in an acutely poisoned person only roughly correlate with clinical signs and symptoms, especially those relating to neurological function. Earlier studies attempted to differentiate between smokers and non-smokers. Attempts have also been made in the literature to divide carbon monoxide poisoning into mild, moderate, and severe based on carboxyhaemoglobin percentage levels and clinical symptoms, but there is no clear clinical consensus or agreement on this issue. The degrees of poisoning have been described as *mild carbon monoxide poisoning:* a carboxyhaemoglobin level of over 10% without clinical signs or symptoms of carbon monoxide poisoning; *moderate carbon monoxide poisoning:* a carboxyhaemoglobin level of over 10%, but under 20-25%, with minor clinical signs and symptoms of poisoning, such as headache, lethargy, or fatigue; and *severe carbon monoxide poisoning:* a carboxyhaemoglobin level of over 20-25%, loss of consciousness, and confusion or signs of cardiac ischaemia, or both. **Population:** For the purpose of this review, we have included adults presenting to healthcare professionals with suspected carbon monoxide poisoning. Although there is no clear consensus on this issue, most studies examining carbon monoxide poisoning and its management use a carboxyhaemoglobin level of 10% or more, or the presence of clinical signs and symptoms after known exposure to carbon monoxide, to be indicative of acute carbon monoxide poisoning. Unless otherwise stated, this definition of acute carbon monoxide poisoning has been used throughout this review. Where appropriate, the terms mild, moderate, or severe have been used to reflect the descriptions of populations in individual studies.

Incidence/ Prevalence

Carbon monoxide poisoning is considered to be one of the leading causes of death and injury worldwide, and is a major public health problem. In 2000, carbon monoxide was the recorded cause of 521 deaths (ICD 9-E986) in England and Wales compared with 1363 deaths recorded in 1985; a trend that has also been observed in the USA. Of the 521 deaths attributed to carbon monoxide poisoning, 148 were accidental and the remaining 373 the result of suicide or self-inflicted injury. Poisoning by carbon monoxide is almost certainly underdiagnosed because of the varied ways in which it can present, and it has been estimated that, in the USA, there are over 40,000 emergency department visits a year; many presenting with a flu-like illness. In 2003, 534 recorded medical episodes in English hospitals involved people suffering from the toxic effects of carbon monoxide. This may be a substantial underestimate if the US experience reflects the true morbidity associated with carbon monoxide poisoning. Studies in the USA have shown that the incidence of accidental carbon monoxide poisoning peaks during the winter months, and is associated with increased use of indoor heating and petrol powered generators, and reduced external ventilation. This seasonal rise in numbers coincides with the annual increase in influenza notifications, and given the similarity in symptoms, many cases of mild carbon monoxide poisoning are probably misdiagnosed.

Aetiology/ Risk factors

People at high risk: People who are most at risk from carbon monoxide poisoning include those with CHD, CVD, or anaemia; pregnant women and their fetus; infants; and the elderly. In people with CHD, experimentally induced blood carboxyhaemoglobin levels of 4.5% shorten the period of exercise before the onset of anginal pain, and the duration of pain is prolonged. In people with anaemia, the oxygen-carrying capacity of the blood is already compromised and therefore they will be more sensitive to carbon monoxide. The elderly are at risk because of existing co-morbidities, such as heart disease or respiratory disease, and because of a reduced compensatory response to hypoxic situations. During pregnancy, a woman's oxygen-carrying capacity is reduced because of an increased endogenous carbon monoxide production and additional endogenous carbon monoxide from the developing fetus, leading to an increased carboxyhaemoglobin concentration. A higher ventilation rate during pregnancy will lead to increased uptake of carbon monoxide at any given carbon monoxide concentration. The fetus is also at risk, and there have been occasional fetal deaths in non-fatal maternal exposures. In the developing fetus, oxygen is released at a lower oxygen partial pressure, and fetal haemoglobin binds with carbon monoxide more quickly compared with adults. Carbon monoxide may be a teratogen where there is a significant increase in maternal carboxyhaemoglobin or where there is moderate-to-severe maternal toxicity. Infants may be more susceptible to the effects of carbon monoxide because of their greater oxygen consumption in relation to adults, and their response and symptoms are more variable. There are recorded instances of children travelling in the same car and having varying symptoms with similar carboxyhaemoglobin levels, or widely varying carboxyhaemoglobin levels with similar carbon monoxide exposure. **Sources of carbon monoxide:** Carbon monoxide is produced by the incomplete combustion of carbon containing fuel, such as gas (domestic or bottled), charcoal, coke, oil, and wood. Potential sources include: gas stoves, fires, and boilers; gas-powered water heaters; car exhaust fumes; charcoal barbeques; paraffin heaters; solid fuel-powered stoves; boilers; and room heaters that are faulty or inadequately ventilated. An overlooked source of carbon monoxide is methylene chloride in some paint strippers and sprays. Methylene chloride is readily absorbed through the skin and lungs and, once in the liver, is converted to carbon monoxide. Methylene chloride is stored in body tissues and released gradually; the carbon monoxide elimination half-life in people exposed to methylene chloride is more than twice that of inhaled carbon monoxide. Natural background levels of carbon monoxide in the outdoor environment range from 0.01-0.23 mg/m^3 (0.009-0.2 ppm), but, in urban traffic in the UK, the 8 hour mean concentrations are higher at about 20 mg/m^3 (17.5 ppm); exposure to this level for prolonged periods could result in a carboxyhaemoglobin level of about 3%.

Prognosis

Prognosis data in carbon monoxide poisoning are inconclusive and contradictory. However, there is general agreement that outcome and prognosis are related to the level of carbon monoxide that a person is exposed to, the duration of exposure, and the presence of underlying risk factors. A poor outcome is predicted by lengthy carbon monoxide exposure, loss of consciousness, and advancing age. In addition, hypotension and cardiac arrest independently predict permanent disability and death. After acute carbon monoxide poisoning the organs most sensitive to hypoxia (the brain and heart) will be most affected. Pre-existing co-morbidities that affect these organs will, to an extent, influence the clinical presentation and the prognosis; an individual with pre-existing heart disease may present with myocardial ischaemia that could lead to infarction and death. The prognosis for people resuscitated after experiencing cardiac arrest with carbon monoxide poisoning is poor. In a small retrospective study, 18 people with carboxyhaemoglobin levels of 31.7 ± 11.0% given hyperbaric oxygen after resuscitation post-cardiac arrest all died. The effects on the brain are more subtle, given that different sections of the brain are more sensitive to hypoxic insults, either as a consequence of reduced oxygen delivery, or by direct effects on intracellular metabolism. Therefore, in addition to the acute neurological sequelae leading to loss of consciousness, coma, and death, neurological sequelae, such as

poor concentration and memory problems, may be apparent in people recovering from carbon monoxide poisoning (persistent neurological sequelae) or develop after a period of apparent normality (delayed neurological sequelae). Delayed neurological sequelae develop between 2 and 240 days after exposure, and are reported to affect 10-32% of people recovering from carbon monoxide poisoning. Symptoms include cognitive changes, personality changes, incontinence, psychosis, and Parkinsonism. Fortunately, 50-75% of people recover within 1 year.

Aims of intervention

To reduce mortality, normalise carboxyhaemoglobin levels, alleviate symptoms, reduce the incidence of delayed neuropsychological sequelae, and reduce cardiovascular morbidity.

Outcomes

Improve conscious levels and cardiovascular parameters; limit neurological sequelae; reduce mortality, hyperoxic seizures, barotrauma associated with hyperbaric oxygen, and serum carboxyhaemoglobin levels.

Methods

BMJ Clinical Evidence search and appraisal March 2007. The following databases were used to identify studies for this review: Medline 1966 to March 2007, Embase 1980 to March 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: for hyperbaric oxygen, only published systematic reviews and RCTs in any language, and containing any number individuals; for interventions other than hyperbaric oxygen, published systematic reviews and RCTs and observational studies in any language, and containing any number individuals. There was no minimum length or follow-up loss required to include studies. We included studies described as" blinded", "open", or "open label". We also did a search for cohort studies on specific harms of named interventions. Studies where the population consisted wholly of children or adolescents have been excluded. Studies and trials were considered in a hierarchical manner with systematic reviews of RCTs being considered as most robust evidence and anecdote the least robust. In the event of no systematic reviews or RCTs being available, observational study data were considered, but only included where it was considered unethical or impractical to conduct an RCT. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table).