TABLE 2

FAULTS IDENTIFIED BY ¡55 DIVERS

Faults Detected by divers	Number	%
Air supply and regulator		
Empty tank	16	29
Air not turned on	42	76
Pillar valve tape still on	16	29
Torn regulator mouthpiece	17	31
Buoyancy jacket		
Power inflator not connected	47	85
Inflator hose mouthpiece	10	18
Emergency dump valve	12	22
Tank loose	33	60
Depth gauge		
Maximum depth indicator not zeroed	20	36

Discussion

Anecdotal data suggest that the average time taken to do a pre-dive check in this study was longer than the time taken to do an "on site" pre-dive check.

These results are disturbing for only 2 divers noted all the faults, only 3 noted the faults that could have potentially fatal consequences (the empty tank, the air supply switched off and the loose dump valve) and that only 14 noted the inadequacy of the air supply. Accident and incident data have shown that morbidity and mortality are associated with inaccurate depth gauges and rapid changes in buoyancy caused by buoyancy jacket problems[5-8] and the majority of divers in this study failed to notice the faults with either the buoyancy jacket or depth gauge.

Ninety six percent of the divers tested did not perform an adequate pre-dive check on the equipment, in particular, how to check the adequacy of an air supply and how to check to see if a buoyancy jacket and depth gauge will function correctly. If these divers could be considered as being representative of recreational divers, because they showed the motivation to attend a diving equipment exhibition that charged an entrance fee, then these data have the obvious safety implication that the majority of recreational divers do not adequately check their equipment before use. With the prevalence of a "failure to check" in diving incidents[4,5,8] an easy to remember, simple guide or a written pre-dive check list is needed. Once devised then its thoroughness will need to be tested.

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CARBON MONOXIDE: FROM TOXIC POISON TO BRAIN MESSENGER

Des Gorman

Introduction

Carbon monoxide (CO) is the most common lethal poison in every community that has been studied.[1] Although many of these poisonings are the result of a deliberate exposure to commit a suicide, toxic exposures to CO are also often the result of both domestic and industrial accidents.[2] In Western societies, the motor vehicle is the major source of CO.[2] Survival after poisoning with CO is frequently associated with neuropsychological deficits, and especially with problems in short-term memory and mood.[3-7] Despite this mortality and morbidity, the toxic mechanisms and the ideal treatment of CO poisoning remain controversial. The received version of CO toxicity is based on hypoxia,[5] and the majority of treatment algorithms are consequently designed to restore blood oxygen content.[5] However, the hypoxic theories of CO toxicity are seriously flawed and when treatment of poisoned patients has been essentially titrated against blood

oxygen content (in fact, it was titrated against the carboxyhaemoglobin (COHb) concentration), many of these patients have developed sequelae from their CO exposure.[7,8] This review of the toxicity of CO is prompted by the need then to:

identify the flaws in the hypoxic theories of CO toxicity;

discourage the treatment of CO poisoned patients with regimens that are designed solely to relieve hypoxia;

examine the recent demonstration of a toxic mechanism which is a good explanation of the delayed effects of CO; and

examine the data that support an important role for endogenous CO in normal neurobiology.

Requirements of a toxic theory for carbon monoxide

A toxic theory for CO must be compatible with both the "natural" history of this poisoning in humans and the demonstrated pathological changes in survivors and lethal poisonings.

A loss of neural function, and particularly confusion, dominate the clinical presentations of CO poisonings.[2-7] Cardiovascular manifestations are much less common. Unless the patient dies, or the presentation is complicated by severe hypoxia arising from apnoea or aspiration of vomitus or loss of airway patency, or other poisons are simultaneously involved, removal of the victim from the CO source is usually followed by recovery and this can probably be accelerated by breathing 100% oxygen.[3-7] Some of these patient recoveries are incomplete and other patients continue to improve after their discharge from hospital (late recoveries).[3-7] Patients who do recover can subsequently relapse or deteriorate (late deteriorations).[3-7] Similar delayed encephalopathies are seen after other forms of brain injury.[9,10]

The neural pathology of CO poisoning has been variously demonstrated by necropsy and neuro-imaging[11-19] to be predominant necrosis of the globus pallidus, areas of the cerebral cortex, hippocampus, cerebellum and substantia nigra. It must be noted that the pathological changes described here have been demonstrated in severely poisoned patients and hence may not be "typical" of the pathology to be found in the majority of those intoxicated. It is also noteworthy that these changes are not identical to those found in hypoxic brain injuries. For example, hippocampal neurons are relatively resistant to hypoxia.[20] There is also a profound difference in the demonstrated resistance of cortical brain function to hypoxia and the extreme sensitivity of this function to CO in rabbits in our laboratory.[21]

Theories of carbon monoxide toxicity

HYPOXIA

The predominant theory of CO toxicity is that it causes hypoxia as a combined result of CO binding to the reduced haeme groups of haemoglobin (Hb) and myoglobin (Mb).[22-31] The Hb that is bound to CO as COHb is unable to form oxyhaemoglobin (OHb) and that OHb which is formed dissociates at relatively lower oxygen tensions in the presence of CO (ie. there is a left shift in the OHb dissociation curve).[32] The poisoning of Hb by CO is argued to be enhanced by a significantly (between 200 and 230 times for human Hb) greater affinity of Hb for CO in comparison with oxygen.[33,34] Although the equilibration of CO with Hb in red blood cells is slower than the oxygen binding to Hb, the formation of COHb is nevertheless complete in a fraction of a second (and hence a pulmonary circulation-time).[35]

The binding of CO to Mb will slow diffusion of oxygen into tissues and is proposed to cause myocardial depression and a consequent hypotensive hypoperfusion of critical organs such as the brain.[12]

While it is not contested that CO binds to Hb and Mb, and that it is possible to measure decreases in tissue and venous blood oxygen tensions in experimental animals[36,37] and humans[38] in the presence of COHb, there are a number of observations that challenge hypoxia as the unique or predominant toxic mechanism of CO.

First, the left shift in OHb dissociation[32] is only significant at a capillary level of oxygen tension if the COHb exceeds 40%, inhibition of brain function is seen at lower concentrations than this in rabbits[21] and in sheep (P. Langstone - personal communication 1994). In these species, brain function is shown to be affected by levels of CO that not only do not cause a capillary-level shift in OHb dissociation, but also that do not cause any change in oxygen delivery, as brain blood flow increases sufficiently to compensate for the decrease in blood oxygen content[21] (P. Langstone - personnal communication 1994).

Second, CO is lethal to rats in hyperbaric oxygen (HBO) conditions in which enough oxygen will be in solution in plasma to meet tissue needs, demonstrating a clear tissue toxicity unrelated to Hb.[39] This conclusion is said to be challenged by the increased survival of animals exposed to CO and given a perfluorocarbon emulsion infusion,[40] but such a challenge is unreasonable.

Third, through a series of exchange-transfusion experiments, all be they of only moderate standard (eg. inadequate controls), it has also been demonstrated that replacement of normal blood cells with those that have been poisoned with CO does not produce any overt toxicity.[41-44]

Fourth, data from other series of animal-model studies are inconsistent with a primary hypoxic mechanism. In those animals in which brain blood flow has been measured during an exposure to CO, flow actually increases[21,38,45-49] such that there is a compensation for the reduced blood oxygen content and a preservation of oxygen delivery.[21] It must be noted that this compensatory maintenance of oxygen delivery, and oxygen availability to tissues, does not prevent a CO-induced disruption of brain function[21] and as CO levels continue to increase, will eventually be overcome.[46] In rats, HBO can be shown to inhibit a CO-precipitated peroxidation of lipids by a mechanism that does not involve an accelerated dissociation of COHb.[50] Also, in rhesus monkeys, the duration and intensity of a CO insult was not critically related to the severity of the consequent abnormality in the cerebral white matter, as would be expected in a "simple" hypoxic insult.[25,26]

Fifth and final, the outcome of patients poisoned with CO does not correlate well with the COHb level measured on arrival at the hospital, indeed, such levels can not even be used to distinguish survivors from non-survivors,[2-7] many patients will develop severe sequelae of CO poisoning despite having no clinical or laboratory evidence of systemic hypoxia,[5] titration of treatment with oxygen against COHb concentration is often unsuccessful in preventing sequelae,[7,8] body stores of CO remain elevated after COHb levels have returned to "normal",[51] and as reported above, the pathological changes seen in severely CO poisoned patients are not identical to those of hypoxic brain injury .[11-19]

TISSUE TOXICITY

The study in rats cited above,[39] demonstrated more than 60 years ago that there is a significant tissue toxicity of CO that is not related to Hb. Since that time a series of tissue toxicity theories of CO have arisen, most have been based on inhibition of the haeme proteins other than Hb and Mb, and in particular, cytochrome C oxidase (CyC-Oase).[33] However, most of these theories rely upon a pre-existing hypoxia to explain both tissue uptake and binding of CO to intracellular proteins. Although many of the intracellular compounds that contain iron or copper will bind CO,[24] under normal circumstances only about 15% of total body CO is extravascular.[52] A significant intracellular hypoxia is "needed" to induce an extravascular redistribution of CO,[52,53] and then, most of the redistributed CO will bind to cardiac[54] and skeletal[55] Mb.

Cytochrome C

Carbon monoxide will bind to the a3 component of reduced CyC-Oase to poison respiration,[56-60] but the affinity for the cytochrome of CO is low in comparison to that of oxygen.[33] For example, direct evidence for CO binding to CyC-Oase in the brain has been obtained in experimental animals, but only in the concurrent presence of COHb levels in excess of 50% and hypotension.[61]

Other haemoproteins

Carbon monoxide will also bind to other reduced haemoproteins such as cytochromes of the P450-type, tryptophan dioxygenase and guanylyl cyclase.[33,62,63] While the significance of CO binding to the former 2 enzymes is uncertain, the over-stimulation of the formation of cyclic-GMP in neurons by exogenous CO[62] may be an essential feature of CO poisoning. This hypothesis, that the acute toxicity of CO is due to an excess of normal endogenous CO functions (which are described later in this paper), is totally conjectural, but a similar argument has achieved credibility in the context of nitric oxide (NO) and ischaemic brain injuries.[64]

Lipid peroxidation

A rat model of CO poisoning[65] has been used to establish a very plausible explanation for the frequent delayed effects of CO (relapses and deteriorations),[2-7] but not for acute toxicity. The first evidence of lipid peroxidation is seen about 90 minutes after rats are exposed to CO (this being due to the displacement of NO from platelets by CO). Rats are probably a reasonable model for human CO exposures in this context.[13,66]

This lipid peroxidation can be inhibited by HBO, but not by 100% oxygen at atmospheric pressure.[50,65,67,68] This is again consistent with clinical experience.[2-7] Although HBO can be shown to antagonise the conversion of nascent enzyme xanthine dehydrogenase to free-radical producing xanthine oxidase,[69,70] the important action of HBO in this context is almost certainly to inhibit the CO-induced accumulation of neutrophils and the adherence of these cells to microvessels.[71] The neutrophils are stimulated by CO to bind to endothelial cells, block blood flow and infiltrate the microvasculature, these cells have been shown to be responsible for the post-CO oxidative brain injury.[71,72] The therapeutic role of HBO proposed here is similarly argued for general ischaemic-reperfusion injuries[73] and in decompression illness.[74]

The ideal dose of oxygen to inhibit post-CO peroxidative injury is not established. In different rat preparations, 101 kPa oxygen had no effect on CO-induced lipid peroxidation, 202 kPa oxygen had some effect and 303 kPa oxygen significantly reduced this peroxidation;[65] whereas, 151 kPa oxygen reduced hydroxyl radical formation after a CO exposure and 252 kPa oxygen actually increased the formation of these radicals.[75] In the latter study, the adverse effect of 252 kPa oxygen was reversed by the concurrent administration of a monoamine oxidase inhibitor.[75] This finding has obvious clinical implications.

Surface adsorption

Because CO is a small molecule and has a high dipole moment as a result of the uneven sharing of

electrons between the carbon and the oxygen atoms, it will readily and tenaciously be adsorbed to solid surfaces (B.A.Hills - personal communication 1987). In many circumstances, CO may then compete successfully for adsorption sites with other reagents. Thus it is possible that reduced rates of reaction could underline the clinical toxicity of CO.

Immune suppression

An observation of uncertain significance in the context of the toxicity of exogenous CO is that the gas alters the immune response, CO induces stress protein-72 production and reduces IL-IB formation in human alveolar macrophages.[76]

OVERVIEW

It is highly unlikely then, with the possible exception of guanylyl cyclase stimulation about which little is known, that none of the theories of CO toxicity outlined here can explain the range of toxic manifestations of this gas in isolation. Indeed, it is likely that different mechanisms underlie the acute toxicity (a primary acute brain syndrome) and the delayed effects (a progressive encephalopathy).

Despite these comments, the received wisdom is that CO is an hypoxic toxin and that the treatment of CO poisoning should be directed at relief of this hypoxia. It is likely that such an approach, when taken to the extreme of titrating treatment against COHb levels in blood, has resulted in some patients suffering otherwise avoidable sequelae.[7,8] The variable response of CO-induced lipid peroxidation to different levels of HBO[65,75] shows that the future of clinical CO research must instead be based on an approach that compares the response of CO poisoned systems and patients to a wide range of different oxygen doses and adjuvant therapy.

The biology of carbon monoxide

Until the normal biological roles of NO were suggested and then confirmed, the endogenous CO produced was considered to be a toxic waste-product of haeme catabolism. It is now clear that this attitude was naive and that endogenous CO is important biologically.

THE BIOLOGY OF NITRIC OXIDE

Nitric oxide is a labile gas that is produced by the catabolism of L-arginine by nitric oxide synthetase (N0S).[77] There are at least 3 forms of NOS, 2 constitutive forms which are variously expressed by endothelium, neurons and astrocytes and an inducible form found in neutrophils and monocytes.

The initial role identified for NO (at the time regarded as a toxic gas) was as part of the mechanism by which macrophages kill tumour cells and bacteria.[78] Since then a wide range of roles have been identified for NO and these include:

action as an endothelial-derived relaxing factor (EDRF)[79] to couple brain blood flow and metabolism[80,81] and also in other vascular actions such as platelet inhibition, cell adhesion, penile erection, the control of the foetal and neonatal pulmonary circulation and the regulation of the expression of vasoconstrictors and growth factors by vascular endothelium;[82-84]

modulation of neuronal behaviour by regulation of cyclic GMP[85,86] and regulation of neural released hormones such as vasopressin and corticotrophin-releasing hormone;[85]

and mediation of ischaemic-reperfusion brain injuries.[64]

THE BIOLOGY OF CARBON MONOXIDE

The demonstration that gaseous NO was a neuronal messenger led to the suggestion that it might be the first of a family of such messengers and not unique.[86] The argument that CO was a member of this family followed the molecular cloning of NOS.[86] The amino acid sequence of NOS is similar to only one other known mammalian enzyme, cytochrome P450 reductase, which is an electron donor to the liver enzymes that metabolise drugs and to haeme oxygenase, the enzyme that metabolises haeme groups to biliverdin and CO.[88,89]

The electron donating function of cytochrome P450 reductase is mediated by 3 cofactors, NADPH, fiavin adenine dinucleotide and flavin mononucleotide, which are also co-factors to NOS and the recognition sites for these co-factors are in the same places on the 2 enzymes.[86]

There are 2 forms of haeme oxygenase; an inducible form (type 1) found in the liver and spleen and a non-inducible form (type 2) found throughout the body and in significant concentrations in specific areas of the brain.[62,90,91]

The more definitive evidence for CO to be an important neuronal messenger has subsequently accumulated and is summarised below:

mRNA for type 2 haeme oxygenase is situated in discrete populations of neurons in rat brain, olfactory bulb, hippocampus, cerebellum, pontine nucleus, habenula, piriform cortex, tenia tecta, olfactory tubercle and islands of Callejae, and in a distribution common to that of cytochrome P450 reductase, delta

aminolevulinate synthase (ALAS), the rate-limiting enzyme in porphyrin biosynthesis, and guanylyl cyclase;[62,86]

most of these brain areas have low concentrations of NOS;

the brain is not a site for red blood cell catabolism[92] and the collocation of all the enzymes necessary to produce both CO and cyclic GMP in these areas of the brain is highly suggestive of a primary messenger role for CO.

there are major discrepancies in the brain distributions ofguanylyl cyclase and NOS, the correlation in the rat brain is much better between concentrations of type 2 haeme oxygenase and guanylyl cyclase;[62]

it is also noteworthy that in those areas of the brain where there is considerable guanylyl cyclase but little type 2 haeme oxygenase (eg. corpus striatum), significant concentrations of NOS can be identified;[93]

inhibitors of type 2 haeme oxygenase, but not inhibitors of NOS, deplete endogenous cyclic GMP in (rat olfactory) neurons;[62]

carbon monoxide binds to the haeme group of guanylyl cyclase in an analogous fashion to NO, increases the formation of cyclic GMP and consequently dilates blood vessels and gut smooth muscle and inhibits platelet aggregation;[89,94-100]

and there is at least a suggestion that type 2 haeme oxygenase blockade inhibits long-term potentiation (LTP) in the hippocampus.[92]

Overall then, all these findings indicate that CO is an important neural messenger associated with physiologic maintenance of endogenous cyclic GMP concentrations.

The (now essentially accepted) biological role of CO outlined above may determine or contribute to the acute toxicity of exogenous CO gas in a manner analogous to that proposed for the "contribution" of NO to ischaemic brain damage.[64] Exogenous CO will be delivered to the brain in solution in plasma and bound to Hb and will diffuse into neurons of all types to bind to available guanylyl cyclase, this in turn will increase the production of cyclic GMP, perhaps to excess and cause a consequent excess of some neuronal activity to the detriment of the cell ("neuronal over-heating"). This is likely to be worse in those areas of the brain where NO is the primary regulator of cyclic GMP as CO is a stable gas in comparison to NO and hence will exist for longer both within the neurons and specifically in combination with guanylyl cyclase.

Summary

The chemically similar gases NO and CO are produced endogenously and are biologically important. Both NO and CO are also toxic when inhaled or absorbed from exogenous sources and this toxicity may arise, in part, from an over-stimulation of those functions which are "normally" regulated by the gases.

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INVESTIGATING DIVING FATALITIES A CASE REPORT

Peter Lewis

Summary

A case report is presented with discussion of the autopsy technique and the evidence needed at the coronial inquest.