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Carbon Monoxide in Healthcare Monitoring Balancing Potential and Challenges in Public Health

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ABSTRACT

Carbon monoxide (CO), a colorless and odorless gas, poses significant risks to public health due to its toxic effects when inhaled at elevated levels. Advances in healthcare monitoring have enabled the detection and management of CO exposure, aiding in early diagnosis and prevention of poisoning. This abstract examines the dual role of CO as both a health hazard and a potential biomarker for certain physiological processes, such as cellular signaling and inflammation. We discuss the challenges of integrating CO monitoring technologies in public health systems, including affordability, accessibility, and data accuracy, while also exploring the opportunities for leveraging these tools in early intervention strategies. A balanced approach is required to harness the benefits of CO monitoring while mitigating its inherent challenges, ensuring its effective application in public health frameworks.

INTRODUCTION

Carbon monoxide (CO) is among the most hazardous gases. This gas can be fatal with extended exposure. A significant level of suspicion, a seasonal aggregation of patients, and a thorough medical history all aid in the diagnosis. Elevated carbon monoxide levels in respiration impact the heart and brain, as well as other vital organs. Consequently, it is understandable why it is referred to as a "silent killer". Scientists are exploring methods to utilise the advantageous properties of carbon monoxide at low levels for therapeutic purposes. The advancements in technology and medicine indicate their potential application in a therapeutic regimen. Controlled exposure to low amounts of carbon monoxide, referred to as CO therapy, has demonstrated potential therapeutic benefits in organ transplantation and ischaemic damage by activating cellular defensive mechanisms. This evaluates the role of carbon monoxide in the human body, its sources, and its prospective applications in disease detection, taking into account sensor technology, standards, ethical considerations, and legal frameworks.

In medical situations, the risk of inadvertent carbon monoxide overexposure during treatment is a concern. Inadequately calibrated equipment, inadequate ventilation, or incorrect dose practices may lead to excessive carbon monoxide delivery, increasing the risk of acute poisoning and compromising patient safety. Carbon monoxide poisoning directly resulted in more than 2,000 suicides and over 500 unintentional fatalities, as reported by the National Health Care Survey done in 2005 by the Centres for Disease Control and Prevention. A substantial preschool carbon monoxide poisoning incident has been effectively managed, averting major harm to children and staff by meticulous care and collaboration .

Carbon monoxide possesses therapeutic advantages, including anti-inflammatory and cytoprotective characteristics, which may be beneficial in addressing inflammatory diseases and complications related to organ transplantation. The medical benefits of CO are underutilised due to limited resources, informational deficiencies, and a lack of clinical investigations. Expanding research on CO-based medicines may yield significant healthcare benefits, challenging its perception as a detrimental toxin. This literature review examines the potential of carbon monoxide in healthcare, highlighting its advantageous benefits when administered in controlled, low dosages, although its hazardous properties.

Methodology:

A comprehensive search was undertaken using Pub med, Scopus, Web of Science, websites (epa.gov, cpsc.gov, verywellhealth.com), newsletters (Medical News Today, Science Daily), and books (Gas Biology Research in Clinical Practice by Karger, Carbon Monoxide in Drug Discovery by Wiley) to conduct this review. Keywords employed included carbon monoxide in healthcare, biomarker, carbon monoxide poisoning, toxicology, monitoring carbon monoxide levels, health effects of carbon monoxide, public health impact carbon monoxide, and carbon monoxide exposure. Owing to the limited availability of research related to the subject of interest, existing literature between 1949 and 2024 was included in the review. Search results were improved by reading the bibliographies of the articles found. It

ensured the topic of CO in healthcare monitoring was thoroughly explored.

Inclusion Criteria:

1) Research on CO in healthcare professions, CO toxicity, clinical trials of CO as medicine
2) Articles discussing the public health impact of CO exposure
3) Studies focusing on both clinical and non-clinical healthcare settings (home care, emergency medicine, hospitals)
4) Original research, meta-analyses, books, newsletters, and .gov websites for statistics
5) English-language publications
6) Studies addressing the balance of benefits and challenges of CO monitoring in healthcare

Exclusion Criteria:

1) Studies focusing on industrial settings not related to healthcare
2) Case reports with insufficient data for generalization
3) Research unrelated to monitoring and healthcare (purely toxicology studies without relevance to healthcare monitoring)
4) Non-peer-reviewed sources (conference abstracts, opinion pieces)

Physiological function of carbon monoxide:

The majority of endogenous carbon monoxide is generated by a process catalysed by the enzyme home oxygenase (HO). Three isoforms of HO exist. Inducible home oxygenase (HO-1) is acknowledged for its role in home oxidation, leading to the production of carbon monoxide and biliverdin. Constitutive home oxygenase (HO-2) facilitates carbon monoxide production and home oxidation. The biological function of HO-3 remains mostly unknown . A small quantity of CO is produced from the degradation of home originating from various homeoproteins, including cytochrome P450. The gut microbiome may potentially generate carbon monoxide . The participation of endogenous carbon monoxide production via the skin may result in innovative medicinal methods. Skin may unexpectedly influence carbon monoxide dynamics, highlighting the intricate interaction of light, chemicals, and human physiology [7]. Skin gas is a complex amalgamation of organic and inorganic volatile compounds released from the skin by dermal glands, circulation, and epidermal processes. Carbon monoxide is one of the components that is excreted through the skin.

Origins of carbon monoxide exposure:

Carbon monoxide exposure can transpire in both outdoor and indoor environments, including workplaces and residences. Specific occupations, such mining and welding, entail a considerable risk of carbon monoxide exposure. Given that paint remover contains dichloromethane, it would be pertinent to investigate whether paint strippers also generate CO during metabolic processes . Vehicle emissions and industrial operations are the primary sources of CO emissions in outdoor environments. Smoking is undeniably detrimental to health. The inhalation rate of tobacco smoke is higher outdoors than indoors . The detrimental impact of smoking on the heart, lungs, and general health is undeniable. It can cause damage in both indoor and outdoor environments. Adolescents are encouraged to establish it as a routine. Individuals exposed to passive smoking have an increased likelihood of developing heart disease, strokes, respiratory infections, and other ailments. Third-hand smoke is an additional concern. It comprises residual particles and fumes from smoking. These substances can be applied to surfaces and subsequently emitted as gases into the atmosphere. Concerns persist regarding third-hand smoking, particularly for tiny children who may encounter polluted surfaces .

Carbon monoxide as a biomarker in medical care:

Exhaled carbon monoxide (exhCO) serves as a diagnostic biomarker for assessing short-term exposure to carbon monoxide (CO). The precise values have been evaluated as potential indicators of inflammation in several conditions, including cystic fibrosis, asthma, pulmonary cancer, chronic obstructive pulmonary disease (COPD), and in critical care or surgical contexts. ExhCO facilitates the assessment of smoking status . Carboxyhemoglobin (COHb) is generated when carbon monoxide (CO) forms a robust coordination bond with the iron atom in haemoglobin (Hb) (Figure 1). A specific biomarker for assessing an individual's exposure to carbon monoxide is carboxyhemoglobin (COHb).

Researchers recommend employing an airtight gas syringe in conjunction with gas chromatography-mass spectrometry (AGS-GC-MS) to quantify the total blood carbon monoxide (TBCO) levels. The TBCO values vary from 1.63 to 104 nmol/mL in headspace, which is analogous to 0.65 to 41.6 μmol/mL in blood plasma. This approach identifies elevated concentrations of dissolved CO, potentially elucidating symptom discrepancies and reducing misdiagnoses. Carbon monoxide can be utilised effectively in healthcare when administered in right quantities. Recent discoveries on the biological advantages of carbon monoxide (CO) have prompted clinical trials to investigate the effects of exogenous CO, administered by CO-releasing molecules (CO-RMs) or inhalation. It encompasses human mitochondrial synthesis preconditioning in patients undergoing aortic valve replacement, pulmonary inflammatory responses post-pyrogen administration, mitigation of post-operative ileus after colon resection for sepsis-induced acute respiratory distress syndrome, management of chronic inflammation in COPD, and improvement of organ tolerance in kidney transplant recipients. Cardiovascular disease may represent the most potential target for carbon monoxide therapy. Nonetheless, numerous mechanisms responsible for the therapeutic actions of carbon monoxide on cardiac tissue require investigation.

Prospects in healthcare:

Since its discovery in 1949, carbon monoxide (CO) has been the subject of extensive scientific investigation, particularly following the revelation that CO is also synthesised endogenously, especially during episodes of heightened erythrocyte degradation . Carbon monoxide seems to mimic the protective role of endogenous heme oxygenase-1 in safeguarding cardiomyocytes against ischemia-reperfusion injury . Revascularisation therapy must commence promptly following cardiac arrest to mitigate myocardial injury. The elevation of inducible HO-1 in the myocardial after ischemia-reperfusion injury is recognised as a crucial protector of cardiac health, likely operating through both carbon monoxide production and the metabolism of toxic . Ischemia-reperfusion injury is caused by the restoration of oxygen to the ischaemic heart . During ischaemic load or sustained elevation of intraventricular pressure, all encapsulated cells, including cardiac cells, produce pro-inflammatory cytokines in response to injury . Exogenous carbon monoxide injection can replicate HO-1 activation, diminish cellular apoptosis, reduce infarct size, and enhance contractility in the rat heart . Carbon monoxide exhibits significant potential for mitigating ischemia/reperfusion injury .

Carbon monoxide is also beneficial in cardiac transplantation. Its anti-proliferative impact on smooth muscle cells diminishes organ rejection and enhances organ survival by activating the recipient's immune response . Carbon monoxide inhibits the proliferation of smooth muscle cells, both directly and indirectly, hence reducing the onset of atherosclerosis . To date, the administration of carbon monoxide (CO) to leverage its beneficial effects on cardiovascular health has been conducted by an inhalation device or a pharmaceutical formulation containing CO-releasing molecules (CO-RMs) .

In liver transplants, carbon monoxide has been demonstrated to enhance survival rates by mitigating ischemia-reperfusion injury, which transpires when blood flow is restored to tissue following a duration of oxygen deprivation. Moreover, CO treatment may facilitate liver regeneration post-injury, establishing it as a prospective therapeutic agent for ailments including cirrhosis and fibrosis. Studies demonstrate that the controlled delivery of CO can alleviate inflammation and oxidative stress, both of which are major factors in hepatic injury. Carbon monoxide (CO) enhances anti-inflammatory processes through pathways such heme oxygenase-1 (HO-1), hence improving cellular viability and reducing hepatic tissue damage.

Musculoskeletal problems currently represent a substantial socioeconomic burden. Rotator cuff tears (RCTs) and rotator cuff disease (RCDs) are the two most prevalent and debilitating conditions, affecting 30 to 70% of the adult population. Therefore, it may be feasible to improve tendon repair post-injury through specific inhibition of CA9/12. The research, sanctioned by the Institutional Review Board of Massachusetts General Hospital and adhering to the Principles of Laboratory Animal Care, demonstrated that carbon monoxide inhalation for 4.5 and 7.5

hours can ameliorate muscle damage caused by ischemia-reperfusion in a murine hind limb model . Mice administered CO exhibited significant decreases in serum and tissue cytokines ($p<0.05$) . CO was further investigated for its potential to enhance rehabilitation following tendon injury. Its capacity to modulate inflammation suggests it could be beneficial in facilitating tendon rehabilitation, crucial for muscle restoration. Carbon monoxide (CO), an endogenous gas transmitter with properties that promote antioxidative, anti-apoptotic, and anti-inflammatory pathways, may influence the start of tendinitis when administered safely and in a regulated manner . Given that CO significantly regulates inflammation, compounds termed CO-RMs may be suitable .

Cancer denotes diseases characterised by unregulated cellular growth and the progression of metastasis. malignancy treatment might vary based on the type and stage of the malignancy. Standard therapies encompass surgical excision of the tumour, pharmacological agents to eradicate or inhibit the proliferation of cancer cells (chemotherapy), and radiotherapy to specifically target and destroy cancer cells. The primary distinction is that immunotherapy enables the body to combat cancer through its immune system, as opposed to targeted treatments that focus on specific molecules implicated in cancer growth and proliferation. Recent developments in cancer treatment include CO-mediated gas therapy, the combined application of CO chemotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), and immunotherapy .

CO-RMs can impede the creation of new blood vessels that supply nutrients to cancer tissues, cause apoptosis in cancer cells, and disrupt the tumour microenvironment to suppress oncogenic progression. Ultimately, CO-RMs can enhance the susceptibility of cancer cells to further therapies, including radiation and chemotherapy, hence increasing the efficacy of these treatments. CO is administered through personalised administration to optimise therapeutic efficacy while minimising adverse effects. A viable approach is to inhibit or eliminate the uncontrolled proliferation of cancer cells, for instance, by inducing cell cycle arrest . A recent study utilising breast cancer cell models revealed that treatment with four readily available CO-RMs—CO-RM-1, CO-RM-2, CO-RM-3, and CO-RM-A1—substantially decreased the excretion of VEGF in these cells, with CO-RM-2 exhibiting the greatest efficacy, followed by CO-RM-3 .

The investigation of CO-RMs as pro-drugs successfully facilitated the delivery of CO to cells and tissues. This exhibited a prospective CO-based pharmaceutical technique. Recent years have seen a growing elucidation of the physiological mechanisms regulating carbon monoxide function in cancer, with investigations into CO-related nanodrugs. It illustrates enhanced application potential in cancer treatment and presents innovative therapeutic strategies .

The accumulation of hepatic lipids is often associated with persistent inflammatory diseases. Carbon monoxide possesses anti-inflammatory characteristics, suppressing the production of cytokines that induce inflammation, such as tumour necrosis factor (TNF-α) and interleukin-6 (IL-6), which may result in hepatic dysfunction and adipose accumulation. Non-alcoholic fatty liver disease (NAFLD) is a condition characterised by the accumulation of fat in the livers of individuals who drink minimal or no alcohol.

Ranging from uncomplicated fatty liver (steatosis) to more severe ailments like non-alcoholic steatohepatitis (NASH), a disorder that may result in liver inflammation, fibrosis, cirrhosis, or carcinoma. Non-alcoholic fatty liver disease (NAFLD) is closely associated with obesity, insulin resistance, type 2 diabetes, and metabolic syndrome. It is typically asymptomatic and discovered inadvertently through blood tests or imaging. Early detection of the illness is crucial to prevent its progression. Carbon monoxide enhances sestrin-2 expression and alleviates hepatic steatosis in non-alcoholic fatty liver disease induced by a methionine/choline-deficient diet . Carbon monoxide-induced protection against cellular apoptosis requires both nitric oxide production and heme oxygenase-1 activity, illustrating for the first time an essential synergy between both substances that provides substantial cytoprotection . Carbon monoxide induces an increase in the sestrin-2 phase, facilitating phagocytosis .

Neuropathy is a clinical condition characterised by dysesthesia and hyperalgesia that is difficult to treat, even with the most potent analgesics. This condition results from the activation of spinal microglia, alterations in the plasticity of cerebral nociceptive pathways, and localised reactions to inflammatory agents [38,39]. Carbon monoxide generated by HO-1 exhibits antinociceptive effects in inflammatory contexts; nevertheless, its relevance in neuropathic pain remains ambiguous . An experiment has shown that carbon monoxide dramatically alleviates neuropathic pain in mice. Following sciatic nerve injury, an interaction occurs between carbon monoxide (CO) and nitric oxide (NO) systems, suggesting that augmenting endogenous production via cobalt protoporphyrin (CoPP), a recognised inducer of heme oxygenase 1, or exogenous production through CO-releasing molecules (CO-RMs) may represent an innovative approach to managing neuropathic pain. Even a single abdominal injection of CO-RM-2 exhibited anti-allodynic efficacy and enhanced the analgesic effects of buprenorphine/morphine, completely alleviating neural pain perceptions .

Obstacles:

A primary barrier in employing CO as a therapeutic agent is the complexity of gas standardisation. It encompasses intricate technical data, calibration procedures, and adherence to regulations. When evaluating CO utilisation for therapy, it is crucial to acknowledge its possible advantages and constraints. No established norms, procedures, or safety issues exist. Consequently, obtaining regulatory approval for CO-based pharmaceuticals may prove challenging. Prior to approving CO treatments for clinical use, regulatory authorities want robust evidence of safety, efficacy, and quality control, hence prolonging the development and regulatory review process.

Future clinical trials are essential to determine the efficacy and safety of treatments for neuropathic pain. Carbon monoxide treatment encompasses several modalities and delivery methods. The lack of established norms complicates consistent execution across diverse situations . Although carbon monoxide demonstrates potential in alleviating neuropathic pain, its limitations underscore the necessity for additional research and careful application. Clinicians must meticulously assess their responsibilities in specific cases.

Despite the promising potential of this therapeutic gas, there exists a deficiency in transdermal CO administration that might be particularly beneficial for wound healing or the treatment of swollen tendons . The evident and hazardous utilisation of gas containers, akin to gas delivery systems for nitric oxide, nitrogen dioxide/oxygen, or xenon, or their absence for the secure and localised generation of these gases, presents an obstacle to the transdermal distribution of gases .

Carbon monoxide, a gas with various characteristics, plays intriguing roles in circulatory functioning. It functions as a powerful vasodilator, inducing relaxation of blood vessels. This characteristic may be advantageous in diseases such as hypertension and ischaemic heart disease. Nonetheless, the obstacles persist: the ongoing administration of carbon monoxide is very difficult due to its fatal consequences. Clinicians must assess the CO prior to administration, and regular monitoring is essential. Excessive consumption of carbon monoxide can adversely affect the heart by diminishing its pumping capacity and affecting its function. Furthermore, chronic smokers are subjected to heightened concentrations of carbon monoxide as a result of cigarette smoke [44,45]. Their values may fluctuate.

Barriers to therapy:

Carbon monoxide is inherently toxic. Substantial dosages inhaled uncontrollably can result in severe brain abnormalities and systemic issues. CO treatment has both opportunities and challenges. Let us analyse the challenges associated with its therapeutic application. Numerous physicians are diligently concentrating on mitigating the incidence and mortality associated with carbon monoxide poisoning, including the reduction of its detrimental effects.

A prominent issue with carbon monoxide (CO) is its inherent danger stemming from its strong binding to haemoglobin (Hb), which forms carboxyhemoglobin (COHb) and diminishes oxygen transport capability. Carbon monoxide treatment poses inherent safety risks, such as the potential exacerbation of hypoxaemia,

cardiac instability, cognitive impairment, and tissue injury. Ensuring patient safety during CO therapy necessitates comprehensive risk assessment, vigilant monitoring, and prompt management of adverse events. Moreover, determining the appropriate dosage for therapeutic purposes might be challenging. Implementing CO-based therapies in hospital environments requires specialised infrastructure, equipment, and trained personnel capable of accurately administering and monitoring CO levels. Ensuring adequate resources and competence for CO therapy may provide logistical challenges, particularly in resource-limited or remote hospital environments. Researchers, healthcare professionals, regulators, and industry stakeholders must collaborate to tackle these difficulties to advance the development, standardisation, and use of CO-based therapies while ensuring patient safety and regulatory adherence.

Prospective trajectories and research avenues:

CO in healthcare presents a possibility to facilitate innovative treatment methodologies and scientific progress within the medical domain. The prospective trajectory may yield numerous pharmaceutical advantages. Further examination of the molecular processes underlying the beneficial effects of carbon monoxide, including its anti-inflammatory, anti-apoptotic, and vasodilatory properties, is feasible. Identifying specific cellular targets and signalling pathways influenced by CO facilitates the development of targeted therapeutics for diseases such as ischaemic injury, neurodegenerative disorders, and inflammatory ailments. The primary challenge in therapeutic applications of controlled CO release is addressed through nano-formulation aimed at specific organs or tissues. Carbon monoxide-related nanodrugs exhibit promise as oncological therapies. These findings present novel prospects for ground breaking treatments.

Another option involves exploring the utilisation of carbon monoxide in biocompatible formats, such as hydrogels or liposomes, through nanotechnology. Solvent, illumination, temperature, and ligand exchange are among the factors that enable CO-RMs to consistently store and release CO payloads . Employing predictive algorithms and biomarkers to identify patients who are most likely to benefit from CO therapy and to customise treatment strategies for maximum safety and efficacy. Utilise collaborative research initiatives and meticulously designed clinical trials to accelerate the conversion of preclinical findings into clinical application, evaluating the safety, efficacy, and long-term effects of CO-based treatments across diverse patient demographics and conditions, while performing comprehensive clinical investigations. Advancing research is crucial to fully exploit the medicinal advantages of CO. Although clinical investigations are rare and the patient population is limited, carbon monoxide remains one of the most promising compounds with substantial potential for the future treatment of certain severe illnesses.

Societal importance:

The societal significance of CO as a therapeutic agent arises from its potential rather than its current widespread use. Investigations into CO-based medicines have demonstrated potential in experimental models and preclinical studies, although clinical translation and widespread acceptance remain in nascent stages. Given that carbon monoxide was formerly regarded as a dangerous pollutant, its therapeutic use constitutes a medical innovation. The anti-inflammatory, cell survival-enhancing, vascular-relaxing, and cytoprotective properties of carbon monoxide render it a potential therapeutic agent for conditions including inflammation, oxidative stress, ischemia-reperfusion injury, and tissue damage. CO therapy, which addresses essential pathophysiological mechanisms, may offer novel therapeutic alternatives and enhance patient outcomes. CO-based medicines possess the capacity to enhance global health by mitigating health disparities, augmenting access to innovative treatments, and reducing disease burdens globally. By enhancing research and promoting equitable access to CO-based pharmaceuticals, the global health community may strive to enhance health outcomes for all individuals.

CONCLUSION

CO is undoubtedly a pertinent subject with both advantages and disadvantages, and scant information regarding its potential benefits has to be explored. Carbon monoxide possesses potential advantages in the treatment of cardiovascular disorders, including vasodilation, anti-apoptotic effects, immunological regulation, and synergistic interactions with other gaseous transmitters. Nonetheless, carbon monoxide is intrinsically hazardous, with extended exposure resulting in sensory impairments. Insufficient evidence substantiates carbon monoxide as a treatment, necessitating prospective clinical trials to determine its efficacy and safety. The absence of standardisation complicates implementation across many contexts. Clinicians must evaluate the potential advantages of CO against its associated hazards. Comprehending the effects of carbon monoxide and tackling associated obstacles can augment its therapeutic potential in cardiovascular disorders. Although investigations into the therapeutic potential of carbon monoxide persist, it must be employed judiciously outside of controlled clinical environments. Advancing knowledge, safe practices, and informed decision-making can mitigate the risks associated with carbon monoxide exposure while fostering ethical scientific inquiry into its therapeutic applications.

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