Title

Hydrogen Sulfide Toxicity: Mechanism of Action, Clinical Presentation, and Countermeasure Development

Journal

Journal of Medical Toxicology, 15(4)

ISSN

1556-9039

Authors

Ng, Patrick C
Hendry-Hofer, Tara B
Witeof, Alyssa E
et al.

Publication Date

2019-10-01

DOI

10.1007/s13181-019-00710-5

Peer reviewed

Journal of Medical Toxicology (2019) 15:287–294
https://doi.org/10.1007/s13181-019-00710-5

REVIEW

Hydrogen Sulfide Toxicity: Mechanism of Action, Clinical Presentation, and Countermeasure Development

Patrick C. Ng[1,2] · Tara B. Hendry-Hofer[2] · Alyssa E. Witeof[2] · Matthew Brenner[3,4] · Sari B. Mahon[3] · Gerry R. Boss[5] · Philippe Haouzi[6] · Vikhyat S. Bebarta[1,2]

Received: 11 January 2019 / Revised: 8 April 2019 / Accepted: 10 April 2019 / Published online: 6 May 2019

Abstract

Introduction Hydrogen sulfide (H_2S) is found in various settings. Reports of chemical suicide, where individuals have combined readily available household chemicals to produce lethal concentrations of H_2S, have demonstrated that H_2S is easily produced. Governmental agencies have warned of potential threats of use of H_2S for a chemical attack, but currently there are no FDA-approved antidotes for H_2S. An ideal antidote would be one that is effective in small volume, readily available, safe, and chemically stable. In this paper we performed a review of the available literature on the mechanism of toxicity, clinical presentation, and development of countermeasures for H_2S toxicity.

Discussion In vivo, H_2S undergoes an incomplete oxidation after an exposure. The remaining non-oxidized H_2S is found in dissolved and combined forms. Dissolved forms such as H_2S gas and sulfhydryl anion can diffuse between blood and tissue. The combined non-soluble forms are found as acid-labile sulfides and sulfhydrated proteins, which play a role in toxicity. Recent countermeasure development takes into account the toxicokinetics of H_2S. Some countermeasures focus on binding free hydrogen sulfide (hydroxocobalamin, cobinamide); some have direct effects on the mitochondria (methylene blue), while others work by mitigating end organ damage by generating other substances such as nitric oxide (NaNO2).

Conclusion H_2S exists in two main pools in vivo after exposure. While several countermeasures are being studied for H_2S intoxication, a need exists for a small-volume, safe, highly effective antidote with a long shelf life to treat acute toxicity as well as prevent long-term effects of exposure.

Keywords Hydrogen sulfide · Countermeasure · Sulfide · Mitochondrial toxin

Background

Hydrogen sulfide (H_2S) is found in petroleum, natural gas, and decaying organic matter [1]. Volcanoes and sulfur springs are areas where significant amounts of H_2S can be found as well [2]. After carbon monoxide, it is the most common cause of occupational gas exposure deaths, particularly in the oil and gas, sanitation, fishing, and farming industries [2, 3]. It has

Supervising Editor: Howard Greller, MD

✉ Patrick C. Ng
patrick.ng@rmpdc.org

[1] Denver Health and Hospital Authority, Rocky Mountain Poison and Drug Center, Denver, CO, USA

[2] Department of Emergency Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[3] Beckman Laser Institute and Medical Clinic, University of California, Irvine, CA, USA

[4] Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, Irvine, CA, USA

[5] Department of Medicine, University of California, San Diego, CA, USA

[6] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Pennsylvania State University, College of Medicine, Hershey, PA, USA

been reported as a means of suicide by combining sulfur-containing household chemicals and acid cleaners to produce the gas [1–3]. In these scenarios, the production of the hydrogen sulfide is rapid and in enclosed environments, such as a car or a small room, can reach deadly concentrations [3]. In 2011, Reedy et al. reported on 45 deaths from chemical suicide involving H_2S with injuries to first responders from 1999 to 2007 [4]. Anderson et al. reported 43 victims of H_2S suicide incidents, 12 of which resulted from secondary exposures of first responders and employees at the coroner's office [5]. With the growing number of chemical suicides from H_2S reported in the USA, the New York State Office of Homeland Security received an advisory note from the Department of Homeland Security titled "Hydrogen Sulfide: A Potential First Responder Hazard" outlining the poison's effects and clues on identifying potential incident sites to prevent secondary exposures [6].

Occupational exposures can occur in industrial settings including tanning, pulp and paper processing, and rayon manufacturing [7]. Multiple occupational exposures resulting in rapid toxicity and a sudden but reversible loss of consciousness described as "knockdown" are reported in the Environmental Protection Agency (EPA) Toxicological Review on Hydrogen Sulfide [7]. These exposures often result in multiple victims as bystanders and first responders attempt to rescue the first victim [8]. In a 2004 report on 52 deaths related to H_2S exposure, Hendrickson and colleagues emphasized the need for proper education and training on H_2S safety [9].

Due to its lethality and ease of production, H_2S is considered a high priority chemical threat in industry and as a potential chemical weapon [6–8]. Its availability and deadly effects make it a favorable candidate for use by terrorist groups [7, 8]. In 2017, a terror plot to create an improvised device to release H_2S was revealed by Australian authorities [10, 11]. That same year, the Transportation Security Administration (TSA) sent out a Security Awareness Message warning of the potential threat of H_2S use in an attack [6]. Its use as a weapon has been documented in several terrorist training manuals including *The Mujahideen Poisons Handbook* [8]. After reviewing such documents, the Department of Homeland Security reported "that the chemical reactions described in the manuals are viable and would yield hydrogen sulfide…" [8].

Currently, there are no FDA-approved antidotes for H_2S poisoning. With the potential for exposure in multiple environmental, occupational, and chemical attack scenarios, the need for an effective countermeasure is evident. An ideal countermeasure is one that is effective and can be easily administered in a small volume (i.e., intramuscularly). Furthermore, an ideal antidote is one that is readily available, stable, and easy to store. We performed a review of the literature focusing on reports on the mechanism of toxicity, clinical presentation, and current developments of a H_2S countermeasure. For the purposes of this manuscript, the term "countermeasure" refers to a treatment modality for hydrogen sulfide. In the several articles referenced in this manuscript, the terms "countermeasure," "antidote," and "treatment" seem to be used interchangeably.

Methods

Search Strategy

A review of the literature was performed and relevant publications were identified by searching the following databases: MEDLINE, Embase, Cochrane Library, Web of Science, and Ovid MEDLINE. Keywords included hydrogen sulfide, antidote, chemical attack, chemical suicide, sulfide, countermeasure, hydrogen sulfide countermeasure, hydrogen sulfide pathophysiology, hydrogen sulfide death, hydrogen sulfide exposure, and hydrogen sulfide animal model. We included publications pertaining to hydrogen sulfide from agencies such as the Centers of Disease Control, World Health Organization, Occupational Safety and Health Administration, and Agency for Toxic Substances and Disease Registry and Environmental Protection Agency. English language limits were applied; animal reports were included. The publication date was limited to articles published from January 1918 to October 2018. The date range chosen was 100 years to try and reasonably capture earlier studies involving hydrogen sulfide as well as more recent literature focusing on countermeasure development.

Study Selection

Four reviewers independently reviewed all titles generated by the search to identify potential relevant articles. Titles and abstracts were initially reviewed; case reports and those articles that did not focus on mechanism of toxicity, clinical presentation, and countermeasure development were excluded. The search was specifically targeted toward studies focusing on the development of countermeasures. Articles discussing the potential benefits of endogenous H_2S were reviewed but are not the main focus of this article. The search detected 466 articles, all of which were screened for relevance to the objective of this manuscript. Fifty-two articles and reports were included.

Basic Science

H_2S is produced endogenously, particularly in the CNS, by cystathionine β-synthase [12]. Human flatus and morning breath have been reported to contain low (average 525 ppb) concentrations of the gas [13]. It has a role in neuromodulation, smooth muscle relaxation, anti-

inflammatory effects, insulin regulation, and in the physiological response to oxidative stress [12, 14].

In 1921, Haggard reported on a series of experiments aimed at understanding how H_2S is transported in the blood following inhalation. Through these experiments, Haggard demonstrated that H_2S is oxidized to non-toxic compounds (sulfite, sulfate, thiosulfate) when mixed with plasma in vitro [15]. The formation of these relatively harmless compounds occurs rapidly which in part explains the rapid clinical improvement that can be seen after removal of victims from H_2S exposure [15–17]. In vivo, most of the H_2S oxidation occurs in the mitochondria via multiple enzymatic processes eventually forming the relatively non-toxic compound, thiosulfate [18, 19].

Despite the rapid oxidation of free H_2S after exposure, other forms can still be detected in arterial blood even after low-dose exposure and toxicity can still develop [16, 17]. Thus, despite the process being rapid, the oxidation of H_2S after exogenous exposure is not complete and the remaining H_2S in vivo is found in dissolved and combined forms. The dissolved forms are present as H_2S gas and the sulfhydryl anion; the two forms that can diffuse between blood and tissue [17]. The proportion of dissolved H_2S is dependent on several factors including pH, temperature, and osmolality [20]. It is also directly proportional to partial pressure [21]. The combined, insoluble forms of sulfide include acid-labile sulfides and sulfhydrated proteins. Both forms trap sulfide in an insoluble state and also play a role in toxicity. For example, sulfide can combine with the iron atom of complex IV of the electron transport chain and can inhibit cytochrome c oxidase [17, 22, 23].

In addition to its effects on cytochrome c oxidase activity, H_2S has several other mechanisms of toxicity. Jiang et al. describes direct toxicity to human inducible pluripotent stem cell–derived neurons, leading to apoptosis [24]. Furthermore, cellular damage from reactive oxygen species, as evidenced by increased activity of protein kinases (JNK and Erk) and generation of F2-isoprostanes, which are prostaglandin-like compounds that serve as markers of oxidative stress, occurs after sulfide exposure [24, 25].

In 2018, Cheung et al. reported on the direct effects of sulfide on myocytes [26]. Sulfide exposure was found to cause dysfunction of myocyte transient outward current and of myocyte inwardly rectifying current. Furthermore, sulfide was found to cause inhibition of various cardiac ionic currents involving sodium and calcium [26]. Cumulatively, these effects on cardiac ion channels and myocyte electrophysiology can contribute to the development of dysrhythmia. This, coupled with anoxia secondary to sulfide toxicity on medullary respiratory neurons, may lead to rapid clinical deterioration and cardiac arrest [26].

H_2S has also been implicated in the activation of transient receptor potential (TRP) channel receptors [27]. TRP channels are a family of ion channels. They serve as chemosensors in various organ systems including the nervous, pulmonary, and cardiovascular systems. There are various subtypes. The A1, M8, and V1 subtypes are the ones most frequently associated with toxicity [27, 28]. Specifically, the A1 subtype of TRP channels responds to toxic signals and the presence of reactive oxygen species. Upon activation of these receptors, calcitonin gene-related peptide (CGRP) is released and can result in vasodilation and hypotension [27–29]. H_2S has been described to activate TRPA1 channels upon exogenous exposure [27–29].

Clinical Presentation

The clinical presentation of H_2S exposures varies and is concentration dependent [1, 3, 7, 24]. At lower concentrations, it is relatively harmless, and classically has a “rotten egg” odor [1–3, 7]. With low concentration sulfide exposure, nonspecific symptoms of headache, nausea, and vomiting can be seen and can rapidly/spontaneously resolve when the exposure is removed [7, 22, 23]. At higher concentrations or with prolonged exposure to the gas, H_2S can cause olfactory paralysis where an individual cannot smell it [7, 8]. At higher concentrations (> 1000 ppm), severe toxicity can result. At these concentrations, H_2S can cause a “knock down,” seizure, CNS depression, cardiovascular collapse, and respiratory failure [7, 8, 22–24]. Several sources including textbooks and agency reports specify that certain concentration cutoffs in parts per million (ppm) correlate with specific clinical features; however, the clinical effects seen are also dependent on other factors such as the duration of exposure as well as the potential for co-exposures to other gases [7]. For example, “gas eye,” or irritation to the eye, has been associated with H_2S exposure and has been reported in individuals exposed to a range of H_2S concentrations (5 to 50 ppm). The development of clinical features like gas eye is partially dependent on the length of exposure as well the concentration of the gas [30]. In a mass casualty incident with exposure to H_2S, a first responder may encounter several victims with varying degrees of toxicity ranging from mild symptoms to severe end organ effects such as headache, nausea/vomiting, sore throat, cough, ocular injury, dysrhythmia, pulmonary edema, apnea, CNS depression, and seizure depending on the concentration and duration of exposure [1, 3, 7]. Furthermore, H_2S exposures have been implicated in the development of pneumonitis, cell mutation, and in the development of neuro-behavioral sequelae [7, 8, 31].

Countermeasure Development

Currently, there are no FDA-approved antidotes for sulfide poisoning. With the discovery of different proposed mechanisms of toxicity of hydrogen sulfide, various

countermeasures have been explored. Given that there are similarities between the proposed mechanisms of toxicity of cyanide and hydrogen sulfide, some of the countermeasures that have been established for cyanide toxicity have also been explored for treating hydrogen sulfide toxicity. We summarize the data regarding potential countermeasures for hydrogen sulfide such as methemoglobin inducers (nitrite), epinephrine, hydroxocobalamin, cobinamide, midazolam, and oxygen. These countermeasures have different therapeutic targets. Methemoglobin induces are targeted toward detoxifying H_2S. Epinephrine, midazolam, and oxygen are targeted toward treating the end organ effects (e.g., PEA, hypoxia, seizure) of the gas. Hydroxocobalamin and cobinamide are targeted toward binding H_2S in vivo.

Methemoglobin Inducers

H_2S has components of its mechanism of toxicity, such as cytochrome c oxidase inhibition that are similar to cyanide [32]. In 1963, Scheler et al. reported anions such as cyanide, sulfide, and azide complex with methemoglobin in vitro and in vivo in mice. Smith et al. explored this further. In 1964, Smith et al. reported data on mice pretreated with sodium nitrite via intraperitoneal injection. Sodium nitrite induces the formation of methemoglobin heme in vivo. After pretreatment with sodium nitrite, the mice were then exposed to the LD_{50} dose for cyanide, sulfide, and azide intraperitoneally. The authors found that 0.75 mmol/kg of sulfide was inactivated by methemoglobin. Furthermore, they compared the efficacy of induced methemoglobinemia on cyanide, sulfide, and azide by calculating the protection index (LD_{50} for nitrite pretreated animals divided by LD_{50} for control animals) for each toxin. They found that pretreatment with methemoglobin had the highest protective effect for cyanide, followed by sulfide [33]. Furthermore, Smith et al. demonstrated that methemoglobin reduces sulfide inhibition of cytochrome c oxidase in vitro [34]. Beck et al. reported that nitrite-induced methemoglobin is an effective means of detoxification of H_2S, but that it is only effective within the first few minutes after the exposure because of how quickly sulfide gets oxidized in vivo [35].

More recently, in 2015, Cronican et al. reported data on mice intoxicated with NaHS administered intraperitoneally. In their study, the authors found, in a dose-dependent manner, that pretreatment with $NaNO_2$ (methemoglobin inducer) via intraperitoneal injection had a protective effect on NaHS intoxication which is in agreement with Smith et al.'s data. Cronican et al. also reported data demonstrating that $NaNO_2$ administered after toxicant administration had no survival benefit in mice intoxicated with NaHS. Furthermore, in contrast to Smith et al., Cronican et al. speculate that nitrite does not exude its protective effect via formation of methemoglobin. They report that $NaNO_2$ in fact serves as a NO donor and that NO is the species that reverses sulfide inhibition of cytochrome c oxidase [36].

In essence, nitrites may be effective in reducing the toxicity of H_2S given as a pretreatment to exposure or shortly after. A recent study suggests that nitric oxide donation from $NaNO_2$ may play a role mitigating the effects of sulfide on cytochrome c oxidase.

Epinephrine

Currently, management for H_2S exposure includes removal from exposure and decontamination, supplemental oxygen therapy, advanced cardiac life support (ACLS), and the use of non-specific treatments such as vasoactive medications and intravenous (IV) fluid [7, 8, 37]. The use of non-specific treatments, like epinephrine, for H_2S toxicity, if shown to be efficacious, may prove to be favorable when compared to other specific countermeasures such as methemoglobin inducers and cobalt-containing compounds that are targeted to bind free H_2S. Epinephrine is readily available in large quantities in both the hospital and prehospital settings [37]. Furthermore, epinephrine can be administered in both intravenous as well as non-intravenous routes (e.g., intra-osseous, intramuscular).

Epinephrine with chest compressions is the treatment of choice of asystole by pulseless electrical activity (PEA) according to the American Heart Association and European Resuscitation Council [37]. As described above, with the direct effects of sulfide on the myocardium and central respiratory centers, asystole by PEA, apnea, and hypoxia can be seen with H_2S toxicity. To counteract these effects of hydrogen sulfide, epinephrine has been explored as a treatment modality for PEA due to H_2S. A recent study demonstrated the efficacy of epinephrine (IV) given 1 min into PEA followed by chest compressions in H_2S (NaHS-intravenous infusion until PEA occurred)-intoxicated rats [37]. NaHS is a commonly used sulfide source in studies involving sulfide exposure [24, 37]. In 2018, Judenherc-Haouzi et al. reported 100% return of effective circulation in the group of animals treated with epinephrine (IV)/chest compressions after H_2S-induced PEA compared to a 0% successful resuscitation rate in the control group. The authors suggest that epinephrine should be further reviewed and considered as an effective countermeasure against H_2S toxicity and raise the question of, if found to be effective, whether or not epinephrine could be systematically offered as an effective countermeasure before PEA from H_2S occurs. Furthermore, the authors highlight the timing of administration of epinephrine 1 min after the development of PEA as a limitation [37].

Hydroxocobalamin

The cobalt-containing antidote for cyanide intoxication, hydroxocobalamin, has been explored as a potential H_2S

countermeasure as well [38–40]. Given H_2S's high affinity for metalloproteinases, the therapeutic target of hydroxocobalamin is to bind/trap H_2S in the blood, thus preventing unbound/free sulfide from diffusing into tissues and causing toxicity.

In 2007, Truong et al. reported data supporting the use of hydroxocobalamin for H_2S toxicity [38]. In this article, the authors described a murine model of H_2S toxicity using NaHS administered via intraperitoneal injection. Animals were divided into 3 groups each containing 30 mice. The groups were delineated by the amount of NaHS administered (LD_{50}, LD_{65}, or LD_{85}). Within each group, animals were further divided into treatment and control groups. In the groups receiving the LD_{50} and LD_{65} dose of NaHS, animals in the treatment groups were administered NaHS intraperitoneally followed by intraperitoneal hydroxocobalamin 2 min post NaHS administration; control animals received only the NaHS. In the group of animals administered the LD_{85} of NaHS intraperitoneally, the animals in treatment subgroups were administered either hydroxocobalamin or nitrite intraperitoneally 2 min post NaHS administration. After 24 h, survival was measured in all groups and the authors found that hydroxocobalamin was effective in decreasing lethality of NaHS in mice. From this study, Truong et al. concluded that hydroxocobalamin may be an effective countermeasure against sulfide poisoning via complexing of H_2S and catalyzing H_2S oxidation.

In 2015, Haouzi et al. reported data on sheep poisoned with NaHS via intravenous infusion and compared rates of cardiac arrest in animals treated with high-dose hydroxocobalamin vs control [39]. In this study, the authors used repeated intravenous infusions of NaHS to induce H_2S intoxication to achieve a concentration of 110 ppm of expired H_2S, which is lethal in this model. Treatment animals were given hydroxocobalamin intravenously 1 min after NaHS infusion. The authors found that high-dose hydroxocobalamin improved hemodynamic parameters and survival (29% survival in control group vs 100% survival in animals that received hydroxocobalamin). Despite these results, the authors reported that animals in the treatment group continued to have elevated lactate concentrations until study end. Furthermore, they reported the kinetics of sulfide were unaltered by hydroxocobalamin administration suggesting the clinical effects seen from the countermeasure may have been secondary to mechanisms other than trapping the free H_2S as previously proposed; however, these potential alternative mechanisms are not yet well described. In contrast to the studies above which suggest potential benefit of hydroxocobalamin use in H_2S toxicity, Brenner et al. found that the mean lethal dose of NaHS was not statistically different between rabbits that received hydroxocobalamin and controls [40].

Cobinamide

Analogs of hydroxocobalamin have also been explored as a potential countermeasure for sulfide poisoning. Cobinamide is the penultimate precursor in hydroxocobalamin synthesis and is reported to have several advantages as a countermeasure that binds H_2S when compared to hydroxocobalamin [40–42]. Cobinamide has 2 binding sites for ligands vs hydroxocobalamin's singular binding site [32]. Also, it more easily undergoes redox reactions and can scavenge toxic chemicals more efficiently compared to hydroxocobalamin. Furthermore, it is more water soluble. In animal models, cobinamide has been shown to improve survival in severe cyanide intoxication [43, 44]. With similarities in the mechanism of toxicity in cyanide and sulfide, cobinamide has been explored as a potential countermeasure for the latter as well [32, 40–42].

In 2014, Brenner et al. reported on the effects of three different ligand forms of cobinamide (aquohydroxocobinamide, sulfitocobinamide, and dinitrocobinamide) vs hydroxocobalamin and saline control in New Zealand white rabbits poisoned with NaHS via intravenous infusion [40]. The rabbits were closely monitored, and the authors reported on survival time and amount of sulfide tolerated with each treatment. The groups treated with all cobinamide forms tolerated higher doses of sulfide infusion and had increased survival times when compared to controls. Of the three cobinamide forms studied, aquohydroxocobinamide was the most effective.

Cobinamide has also been investigated in a large animal model, swine (*Sus scrofa*). In 2017, Bebarta et al. reported data comparing intravenous cobinamide vs hydroxocobalamin or saline control for the treatment of H_2S toxicity. In their study, Bebarta et al. randomized 24 swine into three groups (cobinamide treatment, hydroxocobalamin treatment, saline control). NaHS (8 mg/mL) was infused at 1 mg/kg/min until apnea and then decreased to a maintenance rate to replicate sustained clinical exposure. Treatment was administered 1 min post apnea. Survival was compared between all groups. All cobinamide (8/8)-treated animals survived while none of the control (0/8) or hydroxocobalamin (0/8)-treated animals survived [41].

In a separate study, Ng et al. evaluated intramuscular administration of cobinamide against sulfide poisoning. Similar to the previous study discussed, H_2S toxicity was induced via NaHS intravenous infusion in swine. Treatment animals were administered cobinamide intramuscularly and compared to saline controls. Survival was the primary outcome. The group treated with intramuscular cobinamide had 100% survival compared to 0% survival in the control group [32].

Midazolam

Anantharam et al. report a limitation of countermeasures such as hydroxocobalamin and cobinamide which work by binding H_2S in vivo [31, 45]. The authors reiterate that since free H_2S rapidly dissipates after exposure, drugs that bind free H_2S

in vivo have to be administered shortly after exposure to be effective. Due to such reported limitations, Anantharam et al. explored midazolam as a potential countermeasure in a mouse model that they developed [31]. The authors hypothesized that midazolam would be effective for the treatment of acute H_2S-induced toxicity secondary to its antiepileptic effects [45]. Anantharam et al. exposed mice to 1000 ppm of H_2S and conducted several experiments demonstrating the possible efficacy of midazolam in the treatment of toxicity. They report all mice treated with midazolam during exposure to sulfide survived, while 75% of the animals in the control group died [45]. The authors speculate that the mortality benefit is secondary to the prevention of H_2S-induced seizures. In their earlier studies, Anantharam et al. reported that lethality of sulfide was associated with increased seizure activity and deduce that by preventing seizures, midazolam helps to reduce mortality in mice.

Methylene Blue

To further address limitations associated with countermeasures that work primarily by trapping the rapidly vanishing free H_2S, methylene blue has been studied as a potential countermeasure as well [46, 47]. Methylene blue was first used as an antiseptic and then recognized to be effective in the treatment of methemoglobinemia. Recent studies have demonstrated that methylene blue has antidotal effects for H_2S regardless of the presence of a pool of free H_2S [46, 47]. Antidotal effects are reported to work via multiple mechanisms, one of which is related to methylene blue's redox properties. Methylene blue is reduced to leucomethylene blue which is then readily oxidized back to methylene blue when leucomethylene blue transfers electrons to molecules with higher redox potentials. Such molecules include oxidized metals and reactive oxygen species. This ability for methylene blue/leucomethylene blue to oxidize sulfide, increase hemoglobin's capacity to trap H_2S, restore the cell's redox potential, and restore normal mitochondrial function has been explored by Haouzi et al. in a series of experiments using sheep (*Ovis aries*) [47]. In one protocol, the authors exposed 8 sheep to a lethal dose of NaHS over 10 min. Half of these animals received saline and half received methylene blue during exposure. Animals that did not receive methylene blue rapidly developed cardiac arrest while those that did receive methylene blue maintained steady cardiac output and blood pressure until the end of sulfide infusion. In a second protocol, 13 animals were administered a sublethal infusion of NaHS and methylene blue was administered 3 min after the end of NaHS infusion to 6 animals. Improvement of cardiac contractility, left ventricular ejection fraction, and the pyruvate/lactate ratio was found in animals treated with methylene blue vs saline controls. Furthermore, Judenherc-Haouzi demonstrated that methylene blue restores cardiac myocyte function via restoration of L-type calcium channel activity in murine myocytes in vitro [46].

Oxygen

H_2S-induced hypoxia and apnea have been discussed as contributory factors to end organ dysfunction seen with this exposure [48, 49]. Supplemental oxygen as part of the treatment regimen has been described in addition to other advanced life support measures [50, 51]. Bitterman et al. reported that hydrogen sulfide–poisoned rats treated with oxygen had improved survival compared to control animals. In their experiments, they also treated rats with both oxygen and nitrite. This group had the highest rate of survival [50]. The authors conclude that oxygen is an effective treatment of sulfide poisoning in rats. In contrast, Smith et al. reported that supplemental oxygen given to mice with acute sulfide poisoning did not have any antidotal or protective effects [51, 52].

Conclusion

Hydrogen sulfide (H_2S) exists in two main pools in vivo after exposure: (1) free/soluble H_2S that rapidly dissipates, and (2) a pool of insoluble H_2S that may not be accessible to countermeasures that work by binding the toxin directly. Several potential H_2S countermeasures such as epinephrine with chest compressions, supplemental oxygen, methemoglobin inducers, hydroxocobalamin, cobinamide, midazolam, and methylene blue have been studied and proposed as treatment strategies. While these and other countermeasures are being studied for H_2S intoxication, there continues to be an urgent need for further investigation to discover a small volume, safe, highly effective, stable countermeasure to treat acute toxicity and prevent long-term effects from exposure.

Funding M. Brenner, SB Mahon, GR Boss, P Haouzi, VS Bebarta, TB Hendry-Hofer, AE Witcoff are supported in part by NIH 5U01NS087964-04.

Compliance with ethical standards

Conflict of interest The authors disclose no additional conflicts of interest.

References

1. OSHAFactSheet, U.S. Department of Labor. Available at: https://www.osha.gov/OshDoc/data_Hurricane_Facts/hydrogen_sulfide_fact.pdf. Last accessed: November 9, 2018.

2. Burnett WW, King EG, Grace M, Hall WF. Hydrogen sulfide poisoning: review of 5 years' experience. Can Med Assoc J. 1977;117(11):1277–80.
3. Arnold IM, Dufresne RM, Alleyne BC, Stuart PJ. Health implication of occupational exposures to hydrogen sulfide. J Occup Med. 1985;27(5):373–6.
4. Reddy SJ, Schwartz MD, Morgan BW. Suicide fads: frequency and characteristics of hydrogen sulfide suicides in the United States. West J Emerg Med. 2011;12(3):300–4.
5. Anderson AR. Characterization of chemical suicides in the United States and its adverse impact on responders and bystanders. West J Emerg Med. 2016;17(6):680–3.
6. TSA issues Security Awareness Message on potential use of H2S in terrorist attack. Hazmat/Safety. Bulk Transporter. Available at: https://www.bulktransporter.com/hazmatsafety/tsa-issues-security-awareness-message-potential-use-h2s-terrorist-attack. Last Accessed 5 Nov 2018.
7. Strickland J, Cummings A, Spinnato JA, Liccione JJ, Foureman GL. Toxicological review of hydrogen sulfide. U.S. Environmental Protection Agency, Washington, DC. June 2003. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0061tr.pdf. Last Accessed 30 Mar 2019.
8. Hydrogen sulfide: a potential first responder hazard. New York State office of Homeland Security, Emergency Managers Advisory. Available at: https://info.publicintelligence.net/NYhydrogensulfide.pdf. Last Accessed 5 Nov 2018.
9. Hendrickson RG, Chang A, Hamilton RJ. Co-worker fatalities from hydrogen sulfide. Am J Ind Med. 2004;45(4):346–50.
10. Edinburgh: Blackwood & Sons, Williams J. Australia details 'sophisticated' plot by ISIS to take down plane. New York Times [News], 2017. Available at: https://www.nytimes.com/2017/08/04/world/australia/sydney-airport-terror-plot-isis.html. Last Accessed 14 Mar 2018.
11. McKirdy E, Smith K. Foiled plot to blow up plane, unleash gas revealed in Australia. CNN World. Available at: https://www.cnn.com/2017/08/03/asia/australia-plane-terror-plot-isis/index.html. Last Accessed 5 Nov 2018.
12. Abe K, Kimura H. The possible role of hydrogen sulfide as an endogenous neuromodulator. J Neurosci. 1996;16(3):1066–71.
13. Suarez FL, Furne JK, Springfield J, Levitt MD. Morning breath odor: influence of treatments of sulfur gases. J Dent Res. 2000;79(10):1773–7.
14. Kimura H. Hydrogen sulfide: its production and functions. Exp Physiol. 2011;96(9):833–5.
15. Haggard HW. The fate of sulfides in the blood. J Biol Chem. 1921;49:519–29.
16. Klingerman CM, Trushin N, Prokopczyk B, Haouzi P. H2S concentrations in the arterial blood during H2S administration in relation to its toxicity and effects on breathing. Am J Phys Regul Integr Comp Phys. 2013;305:R630–8.
17. Haouzi P, Sonobe T, Torsell-Tubbs N, Prokopczyk B, Chenuel B, Klingerman CM. In vivo interactions between cobalt or ferric compounds and the pools of sulphide in the blood during and after H2S poisoning. Toxicol Sci. 2014;141(2):493–504.
18. Hildebrandt TM, Grieshaber MK. Three enzymatic activities catalyze oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria. FEBS J. 2008;275:3352–61.
19. Olson KR. A practical look at the chemistry and biology of hydrogen sulfide. Antioxid Redox Signal. 2012;17(1):32–44.
20. Carroll JJ, Mather AE. The solubility of hydrogensulphide in water from 0-90C and pressures to 1Mpa. Geochim Cosmochin Acta. 1989;53:1163–70.
21. DeBruyn WJ, Swartz E, Hu JH, Shorter JA, Davidovits P, Worsnop DR, et al. Henry's law solubilities and Setchenow coefficients for biogenic reduced sulfur species obtained from gas-liquid uptake measurements. J Geophys Res. 1995;100:7245–51.
22. Reiffenstein RJ, Hurlbert WC, Roth SH. Toxicology of hydrogen sulfide. Annu Rev Pharmacol Toxicol. 1992;32:109–13.
23. Haouzi P, Sonobe T, Judenjerc-Haouzi A. Developing effective countermeasures against acute hydrogen sulfide intoxication: challenges and limitations. Ann NY Aca Sci. 2016;1374(1):29–40.
24. Jiang J, Chan A, Ali S, Saha A, Haushalter JK, Lam WL, et al. Hydrogen sulfide—mechanisms of toxicity and development of an antidote. Sci Rep. 2016;6:20831.
25. Eghbal MA, Pennefather PS, O'Brien PJ. H_2S cytotoxicity mechanism involves reactive oxygen species formation and mitochondrial depolarisation. Toxicology. 2004;203(1–3):69–76.
26. Cheung JY, Wang J, Zhang XQ, Song J, Davidyock M, Prado FJ, et al. Methylene blue counteracts H2S induced cardiac ion channel dysfunction and ATP reduction. Cardiovasc Toxicol. 2018;18(5):407–19.
27. Ogawa H, Takahashi K, Miura S, Imagawa T, Saito S, Tominaga M, et al. H2S functions as a nociceptive messenger through transient receptor potential Ankyrin 1 (TRPA1) activation. Neuroscience. 2012;218:335–43.
28. Ujike A, Otsuguro K, Miyamoto R, Yamaguchi S, Ito S. Bidirectional effects of hydrogen sulfide via ATP-sensitive K+ channels and transient receptor potential A1 channels in RIN14B cells. Euro J Pharmacol. 2015;764:4643–470.
29. Steinritz D, Stenger B, Dietrich A, Gudermann T, Popp T. TRPs in Tox: involvement of transient receptor potential-channels in chemical induced organ toxicity—a structured review. Cells 2018 ; 7(8).
30. Beauchamp RO, Bus JS, Popp JA, Boreiko CJ, Andjelkovich DA. A critical review of the literature on hydrogen sulfide toxicity. Crit Rev Toxicol. 1984;13(1):25–97.
31. Anantharam P, Whitley EM, Mahama B, Kim DS, Imerman PM, Shao D, et al. Characterizing a mouse model for evaluation of countermeasures against hydrogen sulfide-induced neurotoxicity and neurological sequelae. Ann N Y Acad Sci. 2017;1400(1):46–64.
32. Ng PC, Hendry-Hofer TB, Garrett N, Brenner M, Mahon SB, Maddry JK, et al. Intramuscular cobinamide versus saline for treatment of severe hydrogen sulfide toxicity in swine. Clin Toxicol. 2019;57(3):189–96.
33. Scheler W, Kabisch R. The antagonistic effect on the acute H2S-toxication in mice by methemoglobin-forming agents. Acta Biol Med Ger. 1963;11:194–9.
34. Smith RP, Gosselin RE. On the mechanism of sulfide inactivation by methemoglobin. Toxicol Appl Pharmacol. 1966;8(1):159–72.
35. Beck JF, Bradbury CM, Connors AJ, Donini JC. Nitrite as an antidote for acute hydrogen sulfide intoxication? Am Ind Hyg Assoc J. 1981;42(11):805–9.
36. Cronican AA, Frawley KL, Ahmed H, Pearce LL, Peterson J. Antagonism of acute sulfide poisoning in mice by nitrite anion without methemoglobinemia. Chem Res Toxicol. 2015;28(7):1398–408.
37. Judenherc-Haouzi A, Sonobe T, Bebarta VS, Haouzi P. On the efficacy of cardio-pulmonary resuscitation and epinephrine following cyanide- and H_2S intoxication-induced cardiac asystole. Cardiovasc Toxicol. 2018;18(5):436–49.
38. Truong DH, Mihajlovic A, Gunness P, Hindmarsh W, O'Brien PJ. Prevention of hydrogen sulfide (H2S)- induced mouse lethality and cytotoxicity by hydroxocobalamin. Toxicology. 2007;242(1–3):16–22.
39. Haouzi P, Chenuel B, Sonobe T. High dose hydroxocobalamin administered after H_2S exposure counteracts sulfide poisoning induced cardiac depression in sheep. Clin Toxicol(Phila). 2015;53(1):28–36.
40. Brenner M, Benavides S, Mahob SB, Lee J, Yoon D, Mukai D, et al. The vitamin b12 analog cobinamide is an effective hydrogen sulfide antidote in a lethal rabbit model. Clin Toxicol(Phila). 2014;52(5):490–7.

41. Bebarta VS, Garrett N, Brenner M, Mahon SB, Maddry JK, Boudreau S, et al. Efficacy of intravenous cobinamide versus hydroxocobalamin or saline for treatment of severe hydrogen sulfide toxicity in a swine (Sus scrofa) model. Acad Emerg Med. 2017;24(9):1088–98.
42. Salnikov DS, Makarov SV, Eldik R, Kucherenko PN, Boss GR. Kinetics and mechanism of the reaction of hydrogen sulfide with diaquacobinamide in aqueous solution. Eur J Inorg Chem. 2014;2014(25):4123–33.
43. Lee J, Mahon SB, Mukai D, Burney T, Katebian BS, Chan A, et al. The vitamin B_{12} analog cobinamide is an effective antidote for oral cyanide poisoning? J Med Toxicol. 2016;12(4):370–9.
44. Bebarta VS, Tanen DA, Boudreau S, Castaneda M, Zarzabal LA, Vargas T, et al. Intravenous cobinamide versus hydroxocobalamin for acute treatment of severe cyanide poisoning in a swine (Sus scrofa) model. Ann Emerg Med. 2014;64(6):612–9.
45. Anantharam P, Kim DS, Whitley EM, Mahama B, Imerman P, Padhi P, et al. Midazolam efficacy against acute hydrogen sulfide-induced mortality and neurotoxicity. J Med Toxicol. 2018;14(1):79–90.
46. Judenherc-Haouzi A, Zhang XQ, Sonobe T, Song J, Rannals MD, Wang J, et al. Methylene blue counteracts H2S toxicity-induced cardiac depression by restoring L-type Ca channel activity. Am J Phys Regul Integr Comp Phys. 2016;310(11):R1030–44.
47. Haouzi P, Tubbs N, Cheung J, Judenherc-Haouzi A. Methylene blue administration during and after life-threatening intoxication by hydrogen sulfide: efficacy studies in adult sheep and mechanisms of action. Toxicol Sci. 2019;168(2):443–59.
48. Truong DH, Eghbal MA, Hindmarsh W, Roth SH, O'Brien PJ. Molecular mechanisms of hydrogen sulfide toxicity. Drug Metab Rev. 2006;38(4):733–44.
49. Guidotti TL. Hydrogen sulfide intoxication. Handb Clin Neurol. 2015;131:111–33.
50. Bitterman N, Talmi Y, Lerman A, Melamed Y, Taitelman U. The effect of hyperbaric oxygen on acute experimental sulfide poisoning in the rat. Toxicol Appl Pharmacol. 1986;84(2):325–8.
51. Smith RP, Kruszyna R, Kruszyna H. Management of acute sulfide poisoning. Archives of Environmental health: An International Journal. 1976;31(3):166–9.
52. Smith L, Kruszyna H, Smith RP. The effect of methemoglobin on the inhibition of cytochrome c oxidase by cyanide, sulfide or azide. Biochem Pharmacol. 1977;26(23):2247–50.