Journal of Medical Toxicology (2019) 15:128–133
https://doi.org/10.1007/s13181-018-0688-y

REVIEW

A Review on Ingested Cyanide: Risks, Clinical Presentation, Diagnostics, and Treatment Challenges

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Received: 30 August 2018 / Revised: 6 November 2018 / Accepted: 19 November 2018 / Published online: 11 December 2018

Abstract

Cyanide, a metabolic poison, is a rising chemial threat and ingestion is the most common route of exposure. Terrorist organizations have threatened to attack the USA and international food and water supplies. The toxicokinetics and toxicodynamics of oral cyanide are unique, resulting in high-dose exposures, severe symptoms, and slower onset of symptoms. There are no FDA-approved therapies tested for oral cyanide ingestions and no approved intramuscular or oral therapies, which would be valuable in mass casualty settings. The aim of this review is to evaluate the risks of oral cyanide and its unique toxicokinetics, as well as address the lack of available rapid diagnostics and treatments for mass casualty events. We will also review current strategies for developing new therapies. A review of the literature using the PRISMA checklist detected 7284 articles, screened 1091, and included 59 articles or other reports. Articles referenced in this review were specific to risk, clinical presentation, diagnostics, current treatments, and developing therapies. Current diagnostics of cyanide exposure can take hours or days, which can delay treatment. Moreover, current therapies for cyanide poisoning are administered intravenously and are not specifically tested for oral exposures, which can result in higher cyanide doses and unique toxicodynamics. New therapies developed for oral cyanide exposures that are easily delivered, safe, and can be administered quickly by first responders in a mass casualty event are needed. Current research is aimed at identifying an antidote that is safe, effective, easy to administer, and has a rapid onset of action.

Keywords Cyanide · Ingestion · Diagnosis · Treatment

Introduction

Cyanide poisoning, whether it be accidental or intentional, remains a major threat to civilians and military personnel worldwide. It is readily available, highly lethal, and easily weaponized. Oral cyanide in particular is the largest threat compared to other routes of exposure, with potassium cyanide (KCN) and sodium cyanide (NaCN) being the most frequently ingested cyanide salt [1, 2]. According to a study reporting data from the National Forensic Service headquarters in Seoul, Korea, there were 255 cyanide poisoning deaths reported from 2005 to 2010, the majority from self-harm [3]. Cyanide remains on the list of potential terrorist threats by various US governmental agencies. One of the most well-known incidents of a large-scale oral cyanide poisoning was the Jonestown massacre, which resulted in more than 900 deaths after drinking cyanide-laced Flavor-Aid [4]. In 1982, seven people in the USA died after ingesting an over-the-counter medication laced with cyanide [5]. In 2015, the Office of the Director of National Intelligence released documents revealing that Osama Bin Laden planned to contaminate food supplies with cyanide [6]. In 2017, a terrorist plot to

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contaminate food supplies with cyanide was foiled and later in that same year, ISIS advised attackers to, "inject food for sale in markets with cyanide poison" [7]. Large-scale poisoning of the food supply could lead to mass casualties if we are not adequately prepared to respond to and do not have adequate supplies of the appropriate antidotes [5, 8].

Parker-Cote and colleagues conducted a systematic review of acute cyanide cases over a 48-year time period [9]. They found 84.3% of the cases were from ingested cyanide, compared to 7.8% inhalation. While the cellular mechanism of oral cyanide is not unique, the toxicokinetics and toxicodynamics of oral cyanide is, thus clinical effects are different than those of inhaled cyanide [10]. In addition, oral exposures to cyanide may result in greater absorption when compared to the inhalational route. With oral exposures, patients can have continued absorption of the toxin once it is ingested. In contrast, inhalational exposures are dependent on the patient's respirations and are limited secondary to the development of apnea from cyanide toxicity. Current FDA-approved therapies are not tailored specifically against oral cyanide poisoning. Furthermore, these therapies are not developed for use by first responders or bystanders in the prehospital setting, creating a major treatment gap. A poll conducted by the American College of Emergency Physicians found that 90% of physicians report hospitals are not well equipped for mass casualties incidents (MCI), citing access to appropriate medications as a major concern [11].

The aim of this review is to evaluate the mechanism, toxicokinetics, and unique aspects of oral cyanide poisoning, highlight the lack of available rapid diagnostics and treatments for mass casualty events with oral cyanide, and review the current strategies for developing new therapies.

Methods

A review of the literature was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Articles indexed in PubMed and EMBASE were identified using the search terms: ingested cyanide, oral cyanide poisoning, cyanide exposure diagnosis, cyanide antidotes, and chemical, biological, radiologic, and nuclear and explosive (CBRNE) preparedness. Articles over the last 60 years were reviewed. The title of the paper was used to determine if the article applied to the topic of interest. More specifically, if the title contained information indicating it was about cyanide toxicity, ingested cyanide, cyanide exposure diagnosis, emergency preparedness, or treatment options, the abstract was reviewed. Upon reviewing the abstract, it was determined if the referenced articles applied to the topic of interest. Individual case reports and non-English articles were excluded from the review. An additional search was conducted through the Centers for Disease Control and Prevention, the Department of Health and Human Services website, NIH Reporter, and the World Health Organization using the search terms cyanide, chemical terrorism, and chemical threats. The search results were evaluated and if the referenced links applied to topic of interest they were included in our review. We found 7284 articles, screened 1091, and used 59 articles or other reports. Articles and reports referenced in this review were specific to risk, clinical presentation, diagnostics, current treatments, and developing therapies.

Mechanism, Toxicokinetics, and Toxicodynamics of Ingested Cyanide

Once absorbed into the blood stream, cyanide equilibrates between the cyanide anion (CN^-) and un-dissociated hydrogen cyanide (HCN) [12]. In this form (HCN), cyanide can easily cross the cell membrane and inhibit multiple enzymes including succinic dehydrogenase, superoxide dismutase, and cytochrome oxidase [12–14]. The latter enzyme is part of complex IV of the mitochondrial electron transport chain. CN^- has a high affinity for the ferric iron (Fe^{3+}) on cytochrome c oxidase, forming a complex that leads to inhibition of the electron transport chain, and thus aerobic respiration [15, 16]. The development of anaerobic metabolism leads to acidemia with hyperlactatemia, a hallmark of cyanide poisoning.

The frequently ingested forms of cyanide, potassium cyanide (KCN) and sodium cyanide (NaCN), are converted to hydrogen cyanide (HCN) in the acidic pH of the stomach [17]. As reported above, this form of cyanide easily crosses the cell membrane and blocks aerobic metabolism within the mitochondria. However, compared to inhaled cyanide exposure, where apnea is one of the first symptoms, the onset of symptoms of oral cyanide exposure is not immediate. Moreover, individuals ingesting cyanide may be unaware they are being poisoned and therefore likely to consume larger amounts prior to developing symptoms [18].

Symptoms and Signs of Cyanide Ingestion

The signs and symptoms of oral cyanide are similar to those of inhaled cyanide; however, the timing and severity differ [12, 18]. Exposure to cyanide via the inhalation route results in symptoms within seconds of exposure, whereas symptoms following ingestion occurs in minutes to hours [19–23]. Relatively few or no symptoms can occur following consumption of small amounts of cyanide [12]. These low-dose exposures frequently cause headache, dizziness, mild confusion, abdominal cramping, nausea, and vomiting. Large-dose exposures eventually lead to dyspnea, respiratory depression, apnea, hypotension, arrhythmias, coma, and seizure. These

large-dose effects can result in irreversible injury and death within minutes of the onset of symptoms [20].

Elevated blood lactate and high venous oxygen levels are commonly seen in cyanide poisoning. However, hyperlactatemia is not specific to cyanide poisoning; other disease processes including sepsis, myocardial infarction, ischemia, drug overdose, and liver failure can present with lactate elevations [21, 24]. Additional abnormal laboratory values consistent with cyanide poisoning also include an elevated anion gap and decreased arterial oxygen levels. Although these abnormal values are not specific to cyanide poisoning, they can aid in proper diagnosis of cyanide poisoning when faced with an incapacitated patient and a MCI.

Diagnostics for Oral Cyanide Poisoning

Quantitative methods to identify cyanide in blood, urine, gastric contents, are available. However, their clinical utility is limited in that these tests take hours or days to result, which can delay treatment. The ability to rapidly identify oral cyanide exposure with a field deployable point of care device would be ideal. Current research is aimed at identifying methods to detect cyanide in blood, plasma, serum, saliva, urine, and even breath [25–28]. According to Jackson and Logue, blood is the ideal matrix for testing for cyanide since cyanide binds to hemoglobin on red blood cells (RBCs) and there is a direct correlation between toxic effects and blood cyanide concentration [27]. Since cyanide binds primarily to RBCs, detection in the plasma and serum is minimal. Jackson and Logue developed a field deployable, rapid diagnostic sensor using fluorescent-based technology. In a rabbit model of cyanide poisoning, their sensor demonstrated the ability to identify cyanide exposure with 100% accuracy in blood samples.

Detection of ingested cyanide in other matrices such as saliva and urine is another, less invasive option. A quick oral swab would provide adequate saliva to detect cyanide exposure; however, there is variability in the amount of saliva in an individual's mouth at a given time making the quantification of cyanide levels challenging [25]. Moreover, smoking can also influence results. Urine cyanide concentrations can also be affected by smoking status. Additionally, due to filtration by the kidneys, urine cyanide levels are much lower than the levels found in the blood [26]. Identifying cyanide exposure in these matrices would require high sensitivity to allow clinicians to identify individuals exposed to levels of cyanide that are likely to suffer from adverse health effects. There is still a need for a cyanide detection device that is simple, durable, rapid, and deployable for field use for oral cyanide disasters and acts of terrorism.

Management and Treatment Challenges

The current treatment regimen for cyanide exposure is supportive care and treatment with intravenous or intraosseous antidote [22, 29, 30]. While this is effective in a large-scale exposure, obtaining venous or osseous access is time consuming and resource intensive [22]. Research aimed at finding the "ideal antidote" for mass casualty settings is ongoing [31]. An "ideal antidote" would have a known mechanism of action, favorably affect the toxicodynamics of the poison, reliably benefit the patient, have rapid onset of action, and be safe even when administered to the non-exposed [22, 31]. Given the potential for cyanide to be used as a chemical threat agent resulting in a large-scale exposure, we propose ease of administration should be included in the definition since, as stated above, obtaining venous access requires skill and expertise.

Additionally, identifying a chemical exposure is primarily symptom based using the "toxidrome" approach, e.g., recognition of a toxic syndrome [32]. While there are methods to identify cyanide exposure, these methods require a significant amount of time to result, thus delaying antidote delivery. Current methodologies aimed at developing a point of care test are in process [27]. Equipping emergency departments and ambulances with point of care testing will allow timely diagnosis of cyanide poisoning, which can decrease time to treatment. Rapid diagnostic tests to identify cyanide exposure can have profound clinical applications, particularly in a mass casualty, resource-limited situation.

Cyanide fits the description of an ideal terrorist weapon as it is, "plentiful, readily available, does not require special knowledge for use, is capable of causing mass confusion, panic, and social disruption, and requires large quantities of specific resources to combat" [33]. The threat of oral cyanide poisoning via food and water supplies is high [33, 34]. In 1992, the Kurdish Workers' Party claimed responsibility for poisoning water tanks in a Turkish Air Force with lethal levels of potassium cyanide [34]. According to the World Health Organization (WHO), local emergency rooms and intensive care units can get overwhelmed and experience shortages of antidotes, such as atropine, following chemical attacks as evidenced by recent chemical weapon use in Syria [35]. Supportive care following ingested cyanide consists of administration of 100% oxygen, followed by activated charcoal, gastric lavage, and intravenous antidote [30, 36]. While these therapies are useful for treating a small number of victims in the hospital, they are not ideal for use in a pre-hospital, mass casualty scenario.

Current FDA-approved treatments for cyanide poisoning fall into three general classes: methemoglobin generators and nitric oxide donors (sodium nitrite, amyl nitrite, and dimethyl aminophenol), sulfur donors (sodium thiosulfate and glutathione), and direct binding agents (hydroxocobalamin and dicobalt edetate) [37, 38]. All three classes of antidotes require

large volume, intravenous administration, have potential stability issues, and adverse effects. Nitrite-based antidotes often cause hypotension and methemoglobinemia, whereas hydroxocobalamin can cause transient hypertension, potentially serious allergic reactions, and red discoloration of the skin and urine, which can interfere with various colorimetric testing.

Antidote Development

Novel antidotes aimed at treating all routes of cyanide exposure, as well as alternate methods of antidote administration including oral, nebulized, sublingual, intramuscular, and subcutaneous are currently being investigated [31–38]. In a mass casualty scenario of oral cyanide poisoning, it is likely there would be various degrees of toxicity. Triaging victims into various categories of exposure and administering antidotes to treat victims based on the degree of toxicity should occur. Examples of this include an oral prophylactic antidote to treat those with minimal or unknown exposure, or an auto-injector for intramuscular delivery of antidote to the critically ill. The advantage of an oral antidote is its potential to prevent the progression of symptoms following suspected cyanide ingestion, allowing first responders to focus their efforts on the more critically ill. Evaluation of oral treatment in rabbits has been reported and is effective for large-dose cyanide ingestions [18]. The benefits of intramuscular injection via auto-injector compared to standard needle and syringe includes improved absorption, ease of administration, dose standardization, and ease of storage/transport [39–43]. Both oral and auto-injector administration would allow for self-administration, further reducing the workload of first responders.

Several agents such as sulfur-transferases, cobinamide, and dimethyl trisulfide (DMTS) are currently under development [18, 44–51]. Sodium nitrite and sodium thiosulfate administered intramuscularly at low doses can be effective, but the current FDA-approved formulation is not packaged to be used this way [51]. Furthermore, neither of these have been tested against oral cyanide.

Multiple federal agencies in the USA are seeking antidotes for chemical agent threats, including cyanide [52, 53]. Since chemical agents cannot be administered to humans, antidotes must be tested for efficacy in animal models and moved forward for FDA approval through the Animal Rule [54]. Under the Animal Rule, antidotes must be tested in a validated animal model with a similar pathophysiology and mechanism of toxicity as to that seen in humans [54]. Furthermore, the ideal animal model for evaluating toxicity and antidote efficacy for cyanide poisoning should have similar physiology compared to humans and allow extrapolation of human dose scaling. Typically, the Animal Rule requires studies to be performed in at least two, reproducible animal models, one of them being a large species, like swine.

Several species are used to test cyanide. Mouse models have frequently been used as the first step in evaluating novel cyanide antidotes [55]. Rabbits have also been used and are more amenable than mice for scaling of doses for human administration and are more amenable to hemodynamic monitoring [46, 47]. Rabbit models of oral cyanide with oral antidotes have been reported and have demonstrated oral antidotes can be effective if given early in the clinical course [18]. The dog model has been used to evaluate efficacy of antidotes; however, due to lower levels of rhodanese compared to other species, they are more susceptible to cyanide than humans [56, 57]. The swine model has been shown to mirror the toxicodynamics of oral cyanide exposures in humans as evidenced by the development of hypotension, apnea, and hyperlactatemia [58].

Animals models are needed to test therapeutics. Small animal models provide a good model to screen therapeutics for general efficacy and gross adverse effects. However, large animal models are better suited to determine efficacy due to their similarities to humans in size, anatomy, and physiology. Also, the large animal model can be more effectively monitored and can provide data on dose scaling for human applications. Dose scaling using smaller animals such as mice and rats is more difficult when compared to larger animals. A recent NIH/DOD report supports rabbits and swine as an optimal species combination for such antidote investigations, with swine having a “digestive system nearly identical to that of humans” [59]. Given these similarities, swine present as an ideal species to use in the pathway towards approval under the Animal Rule. In addition, a model specific to oral cyanide poisoning is needed which is ready for testing therapeutics. A large, swine model has recently been reported [58].

Conclusion

Cyanide is a deadly xenobiotic. Ingestion can lead to a high body burden of cyanide, severe symptoms, and unique toxicodynamics. Many more deaths occur as a result of ingested cyanide compared to other routes of exposure. While many of these deaths are a result of self-harm, cyanide remains a high-risk chemical threat agent [33]. It is readily available, easy to use, and highly lethal making it an ideal chemical weapon [33]. The development of new therapies with clinically relevant animal models specific to oral cyanide should focus on addressing the unique toxicodynamic profile of this route of administration. The development of easily administered and highly effective antidotes for oral cyanide that can be used in a mass casualty setting is important.

Authors' Contributions TH, NG, AE, SM, MB, GB, and VB were involved in the literature and manuscript review. All authors reviewed and approved the manuscript for submission.

Compliance with Ethical Standards

Conflicts of Interest None.

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