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Mechanism and treatment methods of cyanide poisoning

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Abstract. A powerful toxin, cyanide can be ingested accidentally or on purpose. By attaching to cytochrome oxidase in mitochondria, it prevents ATP synthesis and forces cells into anaerobic metabolism even in the presence of sufficient oxygen. Headache, lightheadedness, and dyspnea are the initial signs of cyanide poisoning, which can escalate to seizures and unconsciousness. Sodium nitrite, sodium thiosulfate, and hydroxocobalamin are effective therapies for cyanide poisoning. Research has demonstrated its effectiveness in human and animal models. However, more studies are needed to confirm its efficiency in various cyanide exposure scenarios. While sodium thiosulfate transforms cyanide into the less poisonous thiocyanate, facilitating detoxification, sodium nitrite causes the synthesis of methemoglobin, which sequesters cyanide from cytochrome oxidase. Studies on animals show that intramuscular injections of sodium thiosulfate and sodium nitrite can effectively reverse the effects of cyanide toxicity and improve lifespan. These countermeasures are essential for both treating and averting the deadly consequences of acute cyanide poisoning. This research will discuss the mechanism of cyanide poisoning and its treatment methods.

Keywords: Cyanide poisoning; Mechanism; Treatment methods.

1. Introduction

Cyanide can be found in many different places, such as everyday household items, medical supplies, and industrial products [1]. Sources of cyanide poisoning come from HCN, cyanide salts, and cyanogenic compounds such as amygdalin, which is found in apricot stones. Cyanide poisoning can be accidental or deliberate. It can also come out of drugs like sodium nitroprusside or from incidents like polyurethane foam fires. Symptoms of cyanide poisoning include headache, dizziness, shortness of breath, and vomiting. Progressive symptoms include vertigo, convulsions, paralysis, and unconsciousness. 250 to 325 mg of potassium or sodium cyanide can be fatal in humans. When the blood level is greater than 0.2 mg/mL, it's lethal for people [2]. The victim may seem pink because both the arterial and venous blood continue to have oxygen in them. It's necessary to determine the blood level of cyanide, as treatment may be harmful [2]. The volatile amyl nitrite inhaled can be utilized to quickly oxidize hemoglobin to methemoglobin. Sodium nitrite is then administered intravenously to continue the synthesis of methemoglobin [2]. Thiosulfate will aid in the dissociation of cyanmethemoglobin and the conversion of cyanide to thiocyanate [2]. Another treatment is the administration of cobalt edetate which is combined with cyanide and expelled from our body. Cyanide binds to the Fe^{3+} form of iron in cytochrome c oxidase instead of O_2. By blocking the electrons from being transferred to oxygen at the end of the electron transport chain, this binding stops oxygen from being reduced to water. This blocks ATP synthesis. The toxic dose is greatly influenced by the type of cyanide [1].

The fastest onset of symptoms is caused by cyanide exposures that are inhaled or intravenously administered. Death can happen in a matter of minutes or seconds. The onset of apparent toxicity following intake may not occur for a few minutes until the bloodstream contains sufficient quantities. Because of the special toxicokinetic and toxicodynamic of oral cyanide, high-dose exposures, severe symptoms, and delayed onset of symptoms are all possible outcomes [3]. Oral cyanide symptoms are comparable to those of inhaled cyanide, although they differ in terms of time and intensity [3]. Within

minutes of the beginning of symptoms, these large-dose effects might cause irreparable harm and even death [3].

The mechanisms underlying cyanide toxicity and the strategies for counteracting it are described in the next section. Cyanide inhibits cytochrome oxidase in the mitochondria, which stops ATP synthesis and impairs cellular respiration. Treatments include sodium thiosulfate and sodium nitrite, which neutralize cyanide by converting it into less toxic forms, and hydroxocobalamin, which detoxifies cyanide by attaching to it. These countermeasures are effective, particularly when given intramuscularly. The primary goal of this research is to present the antidotal therapies and the molecular underpinnings of cyanide toxicity, which will be further discussed in the sections that follow.

2. Mechanism

Although cyanide toxicity mechanisms are well-established, they remain incompletely understood. Low amounts of cyanide in the liver are broken down by cyanocobalamin and sulfane reactions, which are then converted to thiocyanate by the enzyme rhodanese. This process is aided by other enzymes such as thiosulfate reductase and 3-mercaptopyruvate sulfurtransferase. These routes are overloaded in acute poisoning, though, which results in the buildup of cyanide. In order to cause harm, cyanide mostly binds to cytochrome oxidase in the mitochondria. This inhibits the electron transport chain and oxidative phosphorylation, stops the synthesis of ATP, and drives cells into anaerobic metabolism even in situations where oxygen levels are sufficient (Figure 1). In general, cytochrome oxidase with mitochondria. This process causes the cessation of cellular respiration.

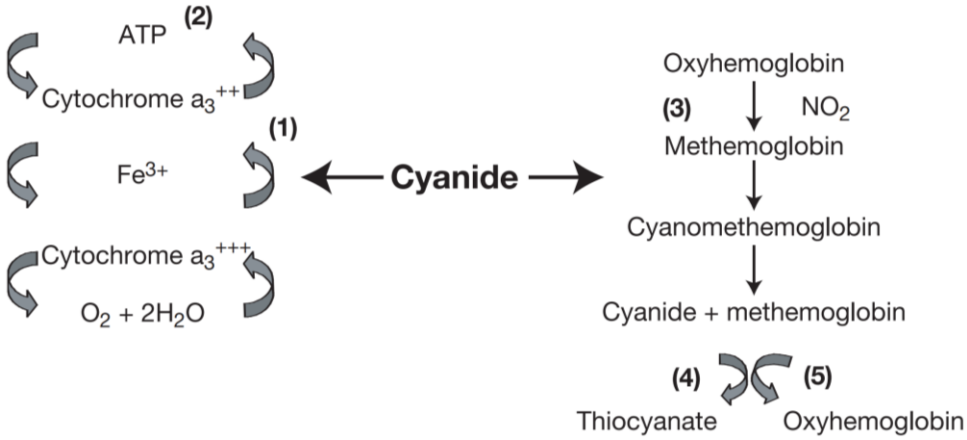

Figure 1. Binding of cytochrome oxidase in mitochondria [1].

Step 1 illustrates how cyanide binds to the cytochrome a_3^+ complex's ferric ion (Fe^{3+}). As demonstrated in step 2, inhibition of the electron transport chain leads to the loss of aerobic metabolism and the production of adenosine triphosphate (ATP). Step 4 involves the kidneys excreting the less poisonous thiocyanate, which is created when the enzyme rhodanase mixes thiosulfate with cyanomethemoglobin. Ultimately, the enzyme methemoglobin reductase transforms methemoglobin back into oxyhemoglobin in step 5.

As shown in Figure 2, complex IV accepts electrons from Cyt c to reduce oxygen to produce water. Cyanide binds tightly with heme. This results in oxygen not being able to bind with hemoglobin. Electron transportation fails in complex IV and ATP can't be synthesized successfully.

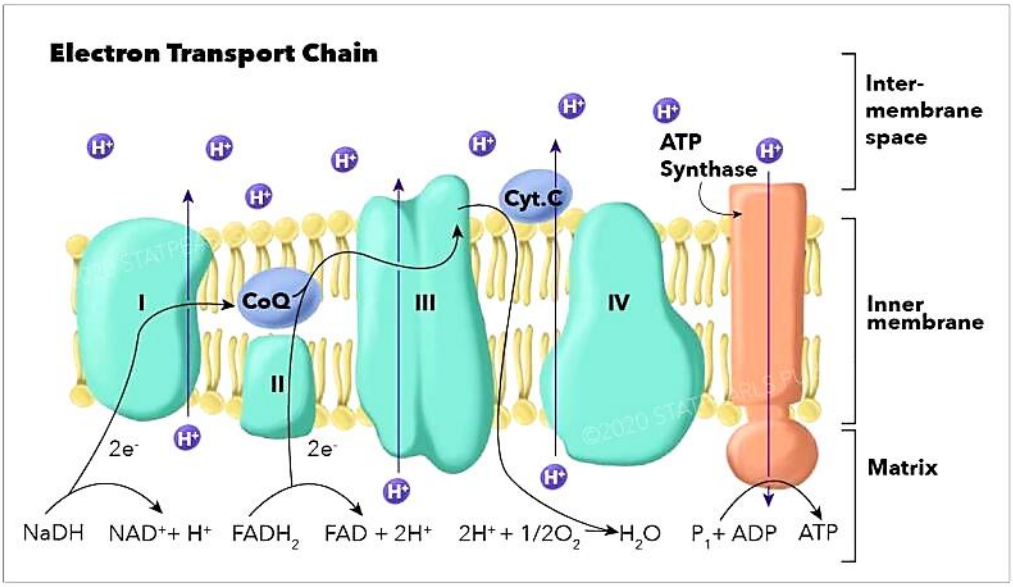

Figure 2. Electron transport chain [4].

3. Treatment

One of the methods is using hydroxocobalamin (vitamin B12a) that is a dark red crystalline powder. Cobalt-containing substances like hydroxocobalamin seem like promising countermeasures for cyanide poisoning [5]. A higher dose is required for an antidote containing cobalt to be effective, the less poisonous it is [5]. Hydroxocobalamin concentrations in biological materials can be determined using a variety of methods, including resonant Raman spectrometry, liquid chromatography, and microbiological assays. However, due to spectrophotometry's simplicity and dependability, it was chosen for this investigation in place of more complex approaches for very high blood concentrations [6]. Dogs in the research received two doses of hydroxocobalamin (70 and 140 mg/kg) [6]. A two-compartment model with first-order distribution and elimination rates was revealed via pharmacokinetic analysis. The volume of distribution and total clearance did not significantly differ across the dosages, although the elimination half-life was shorter at the higher dose. Distribution to interstitial fluids was shown by the volume of distribution being larger than the plasma volume. In comparison to low-dose experiments, the elimination half-life of hydroxocobalamin was significantly shorter. Because of its brief half-life, hydroxocobalamin, which quickly transforms into cyanocobalamin in cases of cyanide poisoning, may require repeated doses or continuous infusion when used in clinical settings. Despite the fact that this study was carried out on non-poisoned dogs, the information can aid direct human treatment [6].

An antidote based on cobalt, hydroxocobalamin is very successful at detoxifying cyanide by binding to cyanide ions and forming cyanocobalamin, which the body subsequently excretes. Research indicates that hydroxocobalamin is effective in treating cyanide poisoning in humans and animals, including instances when smoke inhalation occurs. There is, however, little data on poisonings in humans. A 71% survival rate was seen in a study that examined 14 cases of cyanide salt poisoning treated with hydroxocobalamin, omitting victims who had inhaled smoke. The majority of patients recovered without experiencing long-term problems. The antidote's effectiveness in treating acute cyanide poisoning was demonstrated by the survival of those with initially fatal blood cyanide levels [5]. Additional research has demonstrated the effectiveness of the antidote in situations of hydrogen cyanide inhalation and cyanide salt poisoning. Although hydroxocobalamin is generally well tolerated, chromaturia (discolored urine), skin redness, and transient increases in blood pressure are among the mild adverse effects that have been documented. It has received recognition for being quite safe in comparison to other antidotes for cyanides that can result in methemoglobinemia [5]. To sum up, hydroxocobalamin is a first-line therapy that is both safe and effective for acute cyanide poisoning.

However, further study is required to thoroughly prove its efficacy in treating all forms of cyanide exposure.

Another treatment is by using sodium thiosulfate and sodium nitrite. They are used in the treatment of cyanide poisoning because they neutralize cyanide by changing it into less harmful forms. The exact mechanism of these chemicals' mutual interaction is elucidated by the following four reactions [7]. The enzyme ferricytochrome oxidase is bound by cyanide (NaCN), which prevents it from transferring oxygen during cellular respiration. The symptoms of cyanide poisoning result from this blocking of cellular energy production. As long as the heart beats, the response can be reversed, which is necessary for the antidotal activity to take effect. Hemoglobin (Hb) is changed into methemoglobin (MetHb), a type of hemoglobin in which the iron is in the ferric (Fe^{3+}) state, by sodium nitrite ($NaNO_2$). Methemoglobin can "steal" cyanide from cytochrome oxidase and reverse the harmful inhibition because it has a higher affinity for cyanide ions than the enzyme does. Following this, methemoglobin combines with cyanide ions (NaCN) to create cyanmethemoglobin, a stable and considerably less hazardous substance. Through this process, cyanide is removed from its deadly combination with cytochrome oxidase, allowing cells to resume respiration.

Through the action of the enzyme rhodanese, sodium thiosulfate ($Na_2S_2O_3$) transforms cyanide (NaCN) into thiocyanate (NaSCN), a less poisonous material that the body may safely eliminate. This permanent neutralization of the cyanide ions during the detoxification process improves the overall course of treatment. Cyanmethemoglobin, the resultant molecule, is less toxic and undergoes additional detoxification by converting into thiocyanate, which the body excretes. This reaction is amplified by sodium thiosulfate, which increases the antidote's total potency. If cyanide re-dissociates from cyanmethemoglobin, more doses can be needed. These treatments work well because the production of methemoglobin upsets the equilibrium and permits cytochrome oxidase to function normally, while the production of thiocyanates offers a more long-term detoxifying pathway [7].

The effectiveness of sodium nitrite and sodium thiosulfate has been investigated by using three animal models, including mice, rabbits, and pigs [8]. To evaluate the effectiveness of the antidotes under realistic circumstances, such as prolonged cyanide exposure following therapy, which simulates real-life situations like gas poisoning or ingestion, these models simulate various forms of cyanide exposure.

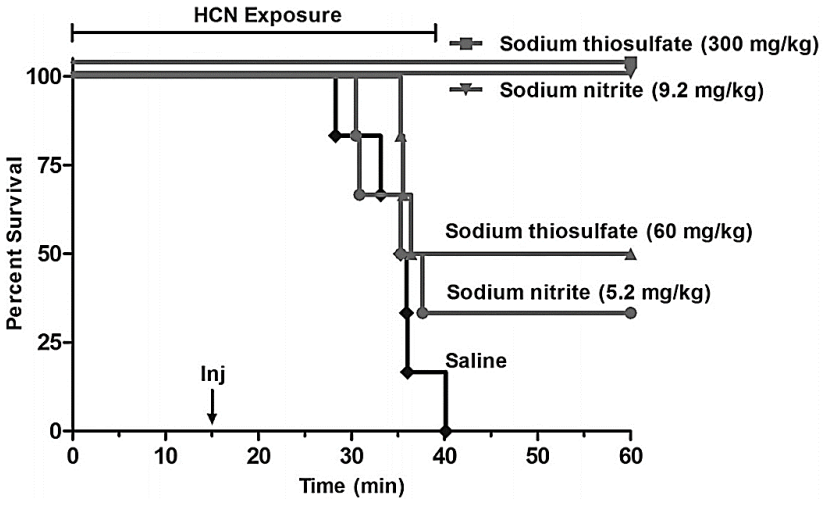

Figure 3. Survival in mouse [8].

For mouse model, mouse was exposed to cyanide gas. After 15 min, they were given intramuscular injection of saline which is represented by black diamonds (Figure 3). Those grey circles represent 5.2 mg/kg sodium nitrite. That inverted triangle represents 9.2 mg/kg sodium nitrite. Grey triangles or squares represent 60 or 300 mg/kg sodium thiosulfate.

After 15 minutes of exposure to hydrogen cyanide gas (587 ppm), mice were given an intramuscular injection of sodium nitrite or sodium thiosulfate, and they were then exposed to the gas again for a

further 25 minutes. Whereas sodium thiosulfate saved 50% of mice at 60 mg/kg and 100% at 300 mg/kg, sodium nitrite saved 33% of mice at 5.2 mg/kg and 100% at 9.2 mg/kg.

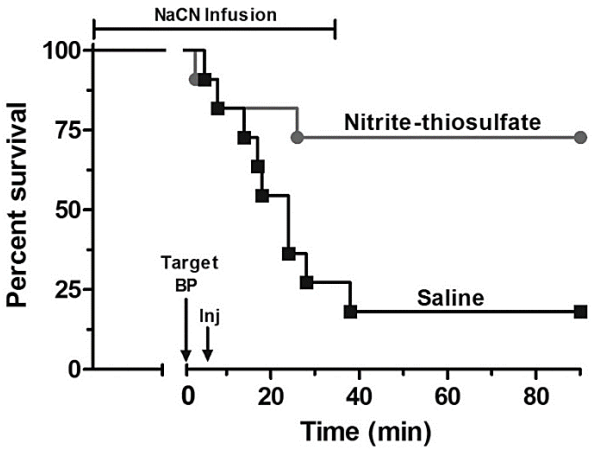

Figure 4. Survival in rabbit [8].

For rabbit model, after the blood pressure dropped to the desired level. Black squares represent the intramuscular injection of saline (Figure 4). Grey circles represent 0.61 mg/kg sodium nitrite and 22.3 mg/kg sodium thiosulfate. Treatment was prompted by cardiovascular failure in the rabbit model. Cyanide injections were given intravenously to rabbits until their blood pressure fell to less than 70% of the baseline. When given intramuscularly, sodium nitrite (0.61 mg/kg) and sodium thiosulfate (22.3 mg/kg) dramatically increased survival over saline-treated controls (2 of 11 survived). This resulted in the rescue of 8 out of 11 rabbits. The effectiveness of the intramuscular method was supported by similar amounts given intravenously, which also proved effective.

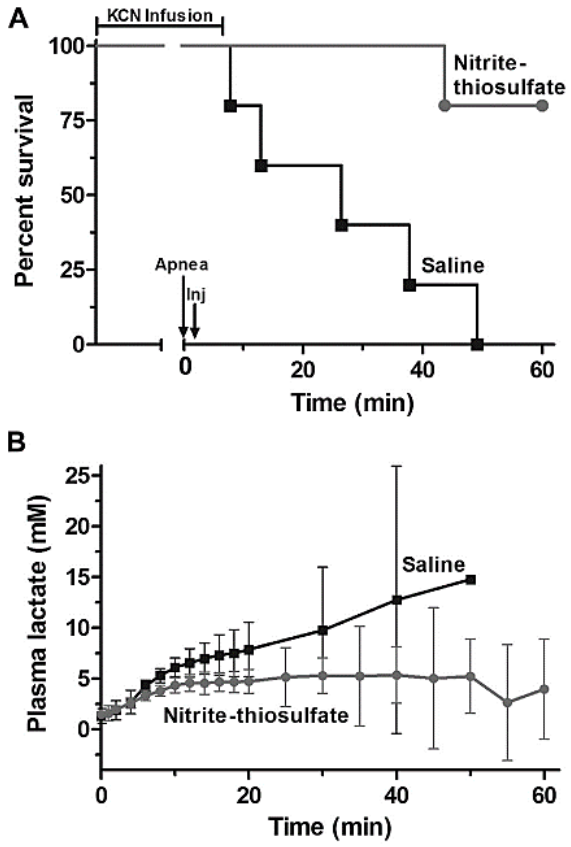

Figure 5. Survival in pigs [8]. (A) Potassium cyanide intravenously. (B) Mean arterial plasma lactate concentration.

The pigs were given an intravenous infusion of potassium cyanide and an intramuscular injection of either saline (black squares) or sodium nitrite (0.69 mg/kg) and sodium thiosulfate (20.8 mg/kg) one minute (grey circles) after the apnea (Figure 5). All five of the control pigs perished, whereas four of the five treated pigs made it. After treatment, the plasma lactate levels of the treated pigs normalized, and the survivors were followed for two weeks without any significant abnormalities. These models showed that both sodium nitrite and sodium thiosulfate work well as cyanide antidotes in a variety of species and that intramuscular administration produced positive results in situations that were similar to actual cyanide poisoning.

4. Conclusion

Because cyanide poisoning acts quickly and fatally, it is considered a serious medical emergency. Effective treatment requires an understanding of the toxicodynamics of cyanide, which largely impairs oxidative phosphorylation by blocking cytochrome oxidase. Because of its quick detoxification of cyanide and safety profile, hydroxocobalamin is the first-choice antidote. Other therapeutic options are provided by sodium nitrite and sodium thiosulfate, which combine to neutralize cyanide by forming methemoglobin and converting it to thiocyanate. The effectiveness of these antidotes when injected intramuscularly is supported by experimental data from animal studies, particularly in emergency situations that mimic real-world cyanide exposure. Even with the encouraging outcomes, more study in human models is necessary to properly determine the best practices for managing different cyanide doses.

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