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Review Article

Cyanide poisoning- an update

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Abstract

Acute cyanide (CN) poisoning leads to deterioration of body functions and often results in death. It can be accidental, suicidal, and at times homicidal. Since the historical period, CN has been the cause for several deaths, including fire accidents, industrial waste leakage, suicides of famous persons, and planned massacres. Several sources can lead to CN poisonings, such as smoke from the fire, mining and other industries, nitriles, and plants. The primary function of CN is to inhibit the cytochrome oxidase a3 enzyme due to the high binding affinity of CN to the ferric iron found in the haem moiety of the cytochrome oxidase a3 leads to uncoupling the mitochondrial oxidative phosphorylation and inhibiting the cellular respiration. Clinical signs and symptoms are primarily dose-related and range from gastrointestinal involvement to coma and death. In addition to decontaminating the poison and essential supportive treatment, effective antidotes are available. Last six years, fifteen Fatalities following CN poisoning were reported at Teaching Hospital, Jaffna. Social support and an adequate legal framework for controlling CN-containing substances could reduce the burden of cyanide toxicity.

Key Words

Cyanide poisoning, Oxidative phosphorylation, cytochrome oxidase, antidote

Introduction

Acute CN poisoning leads to rapid hemodynamic and neurological dysfunction. Most of the time resulted in a fatal outcome (1).CN is an easily accessible, highly lethal, and easily administrable substance. Since ancient times it has remained a threat to the general public and the arm forces worldwide. Ingestion of CN is the standard mode of poisoning rather than the other modes of administration (2). Among the several substances which contain CN, salt KCN and NaCN are the predominant agents that caused deaths (2). Circumstances of CN poisoning are mostly suicidal and accidental, but homicidal poisoning is also not uncommon.

History of cyanide poisoning

In 1704 a German painter Heinrich Diesbach, while he was trying to improve the color on his palette, invented Berlin Blue, which English chemists later called Prussian Blue (3). Eighty years after (1782), the Swedish chemist Carl Wilhelm Scheele mixed the Prussian blue with the acid and discovered HCN. HCN easily condensed and even reacted with water to form strong prussic acid (Hydrocyanic acid) (4).

After the invention of CN, it has been recorded several times in history as a potent killer.

Accidents

Fire accident at Republica Cromanon nightclub in Argentina on 30th December 2004 killed 194 people (5), fire in the Nightclub Lame Horse in Russia destroyed 156 people (6), and fire in Kiss nightclub in January 2013 in the city of Santa Maria in south Brazil where 236 youngsters were killed (7). All these incidents happened CN gas released from burning plastic and related materials (5,6,7). Using CN-containing substances in gold mines and the industrial sector can result in accidental spillage. The cyanide leakage in Argentina (1993) and Romania (2000) resulted in severe environmental disasters (8,9).

Suicides

During world war ll in 1943, Norwegian commandos have launched a successful operation called “Operation Gunner side,” in which they have blasted the Nazi’s heavy water storage with the view of preventing the German atomic bomb production. For this operation, troops were given CN to commit suicide in Nazi capture (10). End of World war ll several Nazi leaders including Odilo Globocknik, Richard Glucks, Hans-Georg Von Friedeburg, Robert Ritter Von Greim, Heinrich Himmler, Martin Borman, and Hermann Goring choose prussic acid (HCN) to end their life (11). German leader Adolf Hitler was biting a CN capsule while shooting himself (12). Hitler’s wife Eva Braun also commit suicide by using CN (11,12). In Sri Lanka, The Liberation Tigers of Tamil Eelam (LTTE) wore a CN capsule around

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their neck to end their life if cornered by the arm forces (13). Several other famous individuals have committed suicide following ingestion of CN.

Homicide

Nazis used Zyclon B pellets (HCN) to kill the Jews on a Mass scale in extermination camps during the Holocaust. Prisoners have been kept inside the chambers, and Zyclon B has been released via the ceiling hole. People died within minutes. Millions of people were killed this way (14). Jonestown Massacre occurred on November 18th, 1978, when 900 members of an American Cult were killed by forcing them to ingest KCN laced flavored drink (15).

Available cyanide containing components

CN is mainly used in mining and other industries such as chemical synthesis, electroplating (Called Potash in Sri Lanka), tanning, metallurgy, printing, agriculture, photography, manufacture of paper and plastics, use of fumigants and insecticides (16). These salts are generated HCN and mixed with strong acids leading to significant risk in industrial workers (17). Waste products from the mining industry produced a vast amount of CN complexes. These chemicals are less toxic than other salts but create a considerable environmental risk (18).

Another group of CN called nitriles is frequently encountered as acetonitrile and propionitriles (19, 20). These chemicals are commonly used in industry as solvents and in households as artificial nail and glue removers (21).

Fire is also a significant source of CN. Many synthetic polymers such as plastics and nylon may release HCN during burning; victims in the fire have the risk of HCN and carbon monoxide poisoning (16). Both HCN and CO are causing hypoxic events. Their effects are addictive and possibly synergistic (22). Some studies suggested that CN is more contributory than CO in household fire (23).

Iatrogenic sources for CN poisoning are nitroprusside in high dose and long duration (24); Laetrile is used as a chemotherapeutic agent, a purified form of natural CN compound amygdalin (25).

CN as cyanogenic glycosides found in plant materials such as Manihot utilissima, Adenia palmata, and Rosacea group plants (26).

Pathophysiology

The primary routes of CN toxicity are inhalation and ingestion. The skin and eyes can absorb the liquid form of CN. After getting absorbed, it will enter the bloodstream and distribute to the tissues and organs very quickly (27). Essentially oxidative phosphorylation is the event that gets impaired due to CN poisoning. ATP (Adenosine triphosphate) provides the major part of the energy needed for cellular function, and oxygen is utilized for ATP formation (28). Transferring electrons from NADH (Nicotinamide adenine dinucleotide) to oxygen is the vital process for ATP production, which happens through a series of electron carriers. The cytochrome oxidase enzyme system catalyzes this in the mitochondria, and impairment of this function occurs due to the inhibition of cytochrome oxidase a3 enzyme by CN. This, in turn, is because of the high binding affinity of CN to the ferric ion found in the haem moiety of the oxidized form of cytochrome oxidase a3. Therefore, uncoupling mitochondrial oxidative phosphorylation and inhibiting cellular respiration, even with enough oxygen in the blood—cellular metabolism shifts from aerobic to anaerobic, leading to subsequent lactic acid production. As a result, the tissues with the highest oxygen requirements (Brain and heart) are the most severely affected organs by acute CN poisoning (29).

CN is not only affecting the cytochrome oxidase a3 enzyme system but also other essential mechanisms, especially in severe toxicity (30). Another school of thought says that decreased cardiac output and cardiogenic shock can happen due to severe vasoconstriction of the coronary artery and pulmonary arterioles (31). The release of biogenic amines may also play an adverse outcome following CN toxicity. Pulmonary edema has also been noted. It is primarily due to left ventricular failure rather than capillary endothelial damage and leak or neurogenic causes (32). However, the exact mechanism related to cardiovascular events is still debatable.

Clinical symptoms and signs

Clinical presentation is dose-related. In small doses, there could be a saltish taste in the mouth, the smell of bitter almonds in the breath, Gastrointestinal symptoms such as salivation, nausea, and vomiting. They can develop shortness of breath, bradycardia, hypotension, arrhythmias, cyanosis, anxiety, vertigo, headache, confusion, drowsiness, paralysis, and eventually coma (26, 28).

In larger doses, patients will get rapid loss of consciousness, twitching of muscles, convulsions, cardiovascular collapse with shock and pulmonary edema, coma, and death. They are often found dead at the scene, pronounced dead on admission to the hospital, or die soon after the access of the hospital (26, 28).

Medical treatment for cyanide poisoning

CN toxicity is rapid, and often there is limited time to treat the patient. Decontamination should be done among all the patients depending on exposure. In inhalational exposure, remove the clothing and other ornaments. In addition to the above dermal decontamination should be done in liquid and solid exposure. Always wear double gloves and mask as several case reports revealed secondary contamination from the victims (33). CN may be exhaled from the affected individual's lungs or contaminated via heavily soaked clothing, skin, or vomitus (33,34).

Gastrointestinal decontamination is very limited due to the rapid onset of toxicity, but some forms of CN have to take a prolonged time for absorption. The patient presented within one hour; it is reasonable to perform orogastric lavage and treat with activated charcoal (35).

Oxygen therapy is very crucial in CN poisoning. 100% oxygen ventilation will increase the tissue oxygen delivery, but in CN poisoning, the main issue is the usage of oxygen rather than the delivery. It might seem useless that give oxygen as a treatment modality (36). However, theoretically, increased oxygen may have a synergistic effect with antidotes. In addition, oxygen may increase the respiratory excretion of CN, stimulate the activation of the other oxidative systems such as enzymes that are not jet poisoned by CN, and activate the rhodanese enzyme indirectly (37, 38). Hyperbaric oxygen treatment for cyanide toxicity is still debatable. Most studies found no positive correlation between hyperbaric oxygen therapy and cyanide toxicity (39,40,41,42). Still, treatment with hyperbaric oxygen is beneficial in carbon monoxide poisoning complicated with CN toxicity (43). Further supportive treatment is needed for other conditions such as acidosis, hemodynamic instability, and convulsions. Usually, seizures are very severe and need aggressive management. In some cases, hemodialysis may be primarily for worsening acidosis and renal involvement (44).

Antidotes

The antidote is defined as "A drug whose mechanism of action has been determined, which can modify either toxicokinetics and/or toxicodynamics of the poison and whose administration to the poisoned patient reliably induces a significant benefit" (45). An ideal antidote should have all the above qualities, and in addition to that, it should not harm when administered to a nonpoisoned patient (allow for errors in diagnosis.). Choosing the antidote is depends on the regional interest. The US is using Lilly Kit ("Taylor Kit" or "Pasadena Kit"), comprised of amyl nitrite, sodium nitrite, and sodium thiosulfate. Some other countries use dicobalt edetate, hydroxycobalamin, and 4-dimethylaminophenol(4-DMAP). Sodium nitrite, sodium thiosulfate, and hydroxycobalamin are administered by intravenous or intraosseous route, amyl nitrite can be used as an inhalational agent, and 4-DMAP is given intramuscularly.

Sodium nitrite and Amyl nitrite: The mechanism of action of this substance is the formation of methemoglobin by mass action and removing the CN from the cytochrome oxidase enzyme. It will lead to the restoration of oxidative phosphorylation. Rhodanase will convert the CN to less toxic thiocyanide and eliminate it via urine (46). Severe hypotension could be a significant adverse effect of nitrites (47).

Sodium Thiosulfate: Donate sulfane sulfur molecule to rhodanase to form the thiocyanide and regenerate the original enzyme (48).

Hydroxycobalamine (Vit B12a): Binds CN quickly and irreversibly form the cyanocobalamin (Vit B12) and is excreted through urine (49). It also binds with nitric oxide (NO), restoring blood pressure in poisoned patients (50).

Dicobalt edetate: It acts as a chelator forming a stable component. It should use only severely poisoned by CN as its potential toxicity by free cobalt (51).

4-Dimethylaminophenol: It is induced the methemoglobin but efficient and faster than sodium nitrite (52).

There are substances under active research and future that can be developed as efficient antidotes such as Alpha-Ketoglutarate, Cobinamide, Dihydroxyacetone, Hydroxylamine, Salfanegen, and S.methyl Mthylthiosulfonate (MTSO) (53,54,55,56,57).

Autopsy findings

The odor of bitter almonds could be noted on entering the autopsy suite while doing the external examination and opening into the body cavities especially opening the stomach. The ability to smell the CN is inherited as a sex-linked recessive trait. Thus, limited people have the ability to smell the poison (26). Bright red or brick red color of the skin, hypostatic areas, blood, muscles, and vascular organs can be observed. Diffusely red mucosa can be seen in the stomach; it can sometimes be observed in the esophagus, duodenum, and jejunum. In addition to the above findings, remnants of CN capsule in the mouth and injury to the gum, tongue, and buccal mucosa in CN capsule biting during suicides and presents of plant materials in the stomach in cyanogenic glycoside toxicity can be noted (26).

Deaths due to cyanide poisoning in Jaffna (2015-2021)

Except a few, all were goldsmiths who succumbed following CN poisoning. A mother (Table 1. Case No 5) has killed her children (Table 1, Case No 6, 7, and 8) by poisoning them with CN and committed suicide with the same method following the 55th day of her husband's (Table 1, case No 4) dismissal by the same poison. A housewife (Table1, Case NO 14) has committed suicide with CN following the husband's (Table1, Case No 13) death due to self-ingestion of CN.

Table 1: Summary of fatal cyanide poisoning cases at Teaching Hospital Jaffna from 2015 to 2021

Case number	Date	Age	Gender	Marital status	occupation	Alcoholism	circumstances
1	12-06-2015	35	Male	Married	Goldsmith	alcoholic	suicide
2	01-08-2016	59	Male	Married	Laborer	alcoholic	suicide
3	23-08-2017	38	Male	Married	Goldsmith	alcoholic	suicide
4	03-09-2017	37	Male	Married	Goldsmith	Occasional alcoholic	Suicide
5	27-10-2017	28	Female	Married	Housewife	Nonalcoholic	suicide
6	27-10-2017	04	Female	-	-	Nonalcoholic	Homicide
7	27-10-2017	02	Male	-	-	Nonalcoholic	Homicide
8	27-10-2017	01	Male	-	-	Nonalcoholic	Homicide
9	19-01-2018	34	Male	Unmarried	Goldsmith	alcoholic	suicide
10	14-11-2018	22	Male	Unmarried	Goldsmith	Nonalcoholic	suicide
11	22-04-2019	46	Male	Married	Goldsmith	alcoholic	suicide
12	01-04-2021	39	male	Unmarried	Goldsmith	Nonalcoholic	suicide
13	07-05-2021	34	Male	Married	Ex goldsmith	alcoholic	suicide
14	07-05-2021	33	Female	Married	Housewife	Nonalcoholic	suicide
15	23-10-2021	49	Male	Married	Ex Goldsmith		suicide
16	28-11-2021	31	Male	Married	An employee of a private firm	alcoholic	suicide

Conclusion

From a toxicological point of view, the death from CN poisoning is rare; however, it is essential to suspect such occurrence in such occupational clusters necessitates the scientific autopsies to be the primary source to detect the cause. Reducing the incidence of self-inflicted deaths warrants more robust sociological support and a need for legalized control of such toxic substances. Failing it, such readily available industrial substances tend to become the household modality of death and a preferred tool for planned homicides due to their inconspicuous nature.

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