

General Approach to Cyanide Poisoning: A Review Article

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Abstract

Cyanide is a rapidly acting, lethal poison that interfere with mitochondrial oxygen utilization. It has many natural, industrial and even household sources. Most common cause of cyanide poisoning is smoke inhalation. Intravenous and inhaled cyanide exposures produce more rapid onset of signs and symptoms than does oral or transdermal ingestions. The clinical presentation varies with the physicochemical form of cyanide, the dose, route of entry, co-toxicants delay since exposure. Central nervous system and cardiovascular system dysfunction are most prominent; also there are nonspecific signs such as nausea, vomiting, headache, dizziness, confusion, coma, seizures, dilated pupils, and abnormal vital signs. Cyanide toxicity expected to have two characteristic symptoms theoretically; those are cherry-red skin and odor of bitter almond from the victims' breath. Cyanide-poisoned patients have an elevated blood lactate concentration. A cutoff point of 8 mmol/L lactate level should be suggested as a diagnostic indicator of cyanide toxicity. Blood cyanide level is the confirmatory test for cyanide poisoning and but it is not routinely performed in most hospitals and may not correlate with toxicity; therefore it cannot guide treatment. The treatment of patients poisoned with cyanide includes supportive care and adjunctive antidotal therapy. Cyanide toxicity is rapidly lethal, so clinicians must stabilize the patient's airway, breathing and circulation first. Antidotal treatment of cyanide poisoning involves three strategies which are binding of cyanide, induction of methemoglobinemia, and use of sulfur donors. Hydroxocobalamin and dicobalt edetate are direct cyanide binding antidotes. In general hydroxocobalamin as first-line antidotal therapy is effective and safe in acute cyanide poisoning. Amily nitrite, sodium nitrite and 4dimethylaminophenol are the antidotes that induce methemoglobinemia. Nitrites are not suitable for fire victims, and those with poor cardiopulmonary reserve. Sodium thiosulfate is a sulfur donor antidote. Recommendation for antidotal treatment strategies in case of cyanide poisoning depends on the availability of antidotes and accuracy of the diagnosis.

Key words: Cyanide, poisoning, antidotes, hydrocobalamin, nitrites

Özet

Siyanür mitokondriyal oksijen kullanımını bozan, hızlı etki eden ölümcül bir zehirdir. Birçok doğal, endüstriyel ve hatta ev içi kaynağı vardır. Siyanür zehirlenmesinin en sık nedeni duman inhalasyonudur. İntravenöz ve inhale siyanür maruziyetleri oral veya transdermal maruziyetten daha hızlı semptom ve bulgu oluştururlar. Klinik presentasyon siyanürün fizikokimyasal formuna, dozuna, alınış şekline, maruziyetten itibaren olan ko-toksiklerin varlığına göre değişir. Santral sinir sistemi ve kardiyovasküler sistem disfonksiyonu ön plandadır; ayrıca bulantı, kusma, baş ağrısı, sersemlik, konfüzyon, koma, nöbet, dilate pupil, ve anormal vital bulgular gibi nonspesifik bulgular olabilir. Siyanür toksitesinde teorik olarak iki karakteristik semptom beklenir; bunlar kiraz kırmızısı deri ve kurbanın nefesinde acı badem kokusudur. Siyanür zehirlenmesi olan hastaların kan laktat konsantrasyonları yükselir. Laktat için 8 mmol/L eşik değer siyanür zehirlenmesi için tanılabilir bir belirteç olarak önerilir. Kan siyanür düzeyi, siyanür zehirlenmesinde doğrulayıcı testtir ancak çoğu hastanede rutin olarak bakılmaz ve toksisite ile korele değildir; bu yüzden tedavide yol gösterici değildir. Siyanürle zehirlenen hastaların tedavisi destek tedaviyi ve yardımcı antidot tedavisini içerir. Siyanür zehirlenmesi hızla ölümcüldür, bu yüzden hekimler önce hastanın havayolunu, solunumunu ve dolaşımını stabilize etmelidirler. Siyanür zehirlenmesinde antidot tedavisi üç stratejiyi içerir bunlar siyanürün bağlanması, methemoglobinemi indüksiyonu ve sülfür donörlerinin kullanımıdır. Hidroksikobalamin ve dikobalt edta direkt siyanür bağlayan antidotlardır. Genel olarak hidroksikobalamin akut siyanür zehirlenmesinde ilk-sırada kullanılan etkili ve güvenilir antidottur. Amil nitrit, sodyum nitrit ve 4dimetilaminofenol methemoglobinemi yapan antidotlardır. Nitritler yangın madurları ve kardiyopulmoner rezervi düşükler için uygun değildir. Sodyum tiosülfat bir sülfür donörüdür. Siyanür zehirlenmesinde önerilen antidot tedavi stratejisi antidota ulaşılabilirliğe ve tanının kesinliğine bağlıdır.

Anahtar kelimeler: Siyanür, zehir, antidot, hidroksikobalamin, nitrit

Introduction

Cyanide is a chemical compound that contains a cyano-group, consists of a carbon atom triple bonded to a nitrogen atom, in combination with other elements such as potassium or hydrogen¹. It is a rapidly acting, lethal poison

that interfere with mitochondrial oxygen utilization². Cyanide used as a method of execution since ancient times; and with the media news about its repetitive use as a suicide agent last year in Turkey, attention to cyanide poisoning was increased. This paper aims to appraise the evidence base for the clinical management of cyanide toxicity.

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Etiology

Cyanide has many natural, industrial and even household sources. Most common cause of cyanide poisoning in Western countries is smoke inhalation³. Cyanide is formed during the incomplete combustion of nitrogen containing materials, such as wool, silk and melamine which are increasingly being used in homes⁴. Therefore, inhalation of toxic fumes in domestic fires can be the cause of cyanide toxicity among fire victims⁴.

Occupational exposures account for a significant number of cyanide poisonings. Metal extraction in mining, electroplating in jewelry production, photography, plastics and rubber manufacturing and rodent pesticide and fumigants have all been implicated in cyanide poisonings⁵. Industrial consumption of cyanide can be either via inhalation or skin absorption. Ingestion of cyanide compounds either with suicidal intent or accidentally were also reported⁶.

Iatrogenic toxicity due to administration of cyanide-group containing medications such as sodium nitroprusside (SNP), a medication used in the treatment of hypertensive emergencies, was also reported. Impaired renal functions, prolonged infusion duration and/or high doses of SNP infusion were defined risk factors for SNP induced cyanide toxicity⁷.

There are also some food that contain cyanogenic glycosides, such as amygdalin, in their pits and seed⁵. Bitter almond, cherry laurel, apricot, plum, peach, pear, and apple are some examples. Although not a common cause of poisoning, those natural sources can produce cyanide toxicity when taken in large quantities¹.

Pathophysiology

Cyanide causes rapid toxicity upon exposure, in large part due to the inhibition of cytochrome-c oxidase-dependent cellular respiration⁸. It avidly binds to the ferric ion (Fe³⁺) of cytochrome oxidase a₃ and inhibiting this final enzyme in the mitochondrial cytochrome complex. Cells cannot utilize oxygen because of their poisoned electron transport chain; and as a result cellular pseudohypoxia and acidosis occur⁸. Also a small amount of cyanide may bind to the ferrous (Fe²⁺) iron of hemoglobin, to form cyanohemoglobin, which is unable to transport oxygen, thereby further exacerbating tissue hypoxia⁹.

Cyanide is rapidly absorbed through the respiratory tract and mucous membranes, and it can also be absorbed through the gastrointestinal tract and skin. Intravenous and inhaled cyanide exposures produce more rapid onset of signs and symptoms than does oral or transdermal ingestions because they provide fast diffusion and direct distribution to target organs via the bloodstream¹⁰.

Cyanide metabolism and neutralization involve a number of mechanisms. The primary endogenous mechanism of cyanide detoxification is metabolism in the liver by rhodanese

to thiocyanate, which is a nontoxic compound excreted in the urine. Second and a minor pathway for cyanide detoxification involves hydroxocobalamin, the precursor to vitamin B₁₂, to form cyanocobalamin. It is also excreted in the urine. Third, small amounts of cyanide that are not detoxified can be excreted unmetabolized in breath, urine, and sweat¹⁰.

Clinical presentation

The clinical presentation of cyanide poisoning varies with the physicochemical form of cyanide, the dose, route of entry, co-toxicants (carbon monoxide, etc.) and delay since exposure. Because of being more sensitive to hypoxia, central nervous system and cardiovascular system dysfunction are most prominent. Nonspecific signs of cyanide poisoning are nausea, vomiting, headache, dizziness, confusion, coma, seizures, dilated pupils, and abnormal vital signs¹¹. It causes an initial tachypnea and hyperpnea with tachycardia and hypertension that progress to apnea and cardiovascular collapse with dysrhythmias soon¹¹. Cyanide toxicity expected to have two characteristic symptoms theoretically; those are cherry-red skin and odor of bitter almond from the victims' breath¹². However, odor is not a valid assumption because half of the population unable to detect this odor¹². Also, presence of cherry-red skin upon initial presentation, which is a result of increased venous hemoglobin oxygen saturation, has not a predictable incidence¹³.

Survivors of severe cyanide toxicity may develop neurologic sequel including Parkinsonism, dystonia and dyskinesia, reflective of the involvement of the structures within the basal ganglia¹⁴. Neuroimaging may demonstrate radiologic changes several weeks after the exposure. Effects of acute cyanide poisoning on brain structure and function is unpredictable¹⁴. Resolution of symptoms is variable, and treatment is supportive.

Diagnosis

Routine laboratory evaluation in the potentially poisoned patient should include fingerstick glucose concentration, acetaminophen and salicylate levels to rule common coingestions, electrocardiogram and pregnancy test in women of childbearing age. Specific testing in cases of potential cyanide poisoning should also include the basic chemistries and arterial blood gas to assess for high anion gap metabolic acidosis¹⁵.

Cyanide-poisoned patients have an elevated blood lactate concentration. Multivariate analysis conferred hyperlactacidemia as the lone factor which significantly predicted cyanide poisoning at an odds of 73.0 (5.7-936.1)¹⁶. A cutoff point of 8 mmol/L lactate level should be suggested as a diagnostic indicator of cyanide toxicity¹⁶. In the setting of smoke inhalation, a plasma lactate > 10 mmol/L should be more sensitive¹¹.

A narrowing of the venous-arterial PO₂ gradient, in other words venous hyperoxia, may be seen in the cyanide-poisoned patient. However, this is a nonspecific finding and can result from other inhibitors of oxidative phosphorylation, such as carbon monoxide, hydrogen sulfide, and azides⁹. Therefore carboxyhemoglobin and methemoglobin levels should be checked, particularly if there is any concern for concomitant exposure. Cyanide poisoning can also cause renal failure, hepatic failure, rhabdomyolysis and pulmonary edema; so relevant studies should be obtained as indicated.

Blood cyanide level is the confirmatory test for cyanide poisoning and but it is not routinely performed in most hospitals and may not correlate with toxicity; therefore it cannot guide treatment¹¹. Thus, cyanide poisoning is an uncommon entity and making the diagnosis requires a high index of clinic suspicion based on history and presentation.

Management

The treatment of patients poisoned with cyanide includes supportive care and adjunctive antidotal therapy.

General treatment

Cyanide toxicity is rapidly lethal, so clinicians must stabilize the patient's airway, breathing and circulation first. Intravenous access must be established and cardiac monitoring must be started. Intubation is usually required and high-flow oxygen should be administered regardless of pulse oximetry reading because %100 oxygen may enhance the effectiveness of antidotal therapy by competing with cyanide for the cytochrome oxidase binding sites¹. Mouth to mouth resuscitation must be avoided in case of suspected cyanide toxicity. Supportive care, rapid IV boluses of isotonic fluid and vasopressors as needed for treatment of hypotension and benzodiazepines for treatment of seizures, should be performed. Hyperbaric oxygen has been advocated as a potential adjunct for cyanide toxicity; however, the evidence for its efficacy in this situation is limited and conflicting³.

Decontamination

Decontamination is an important step for the management of patients with cyanide poisoning. Patients poisoned by cyanide through inhalation must be removed from source into fresh air and contaminated cloths must be taken off and appropriately discarded. In case of dermal exposures skin must be washed with soap and water or water alone, eyes must be irrigated with saline and contact lenses must be removed¹.

In cases of oral ingestion gastrointestinal decontamination should be performed rapidly. Activated charcoal of a single dose (1 g/kg, max 50 gr) may be administered if the

victim is alert and ingestion occurred within 1 hour⁹. Emesis should not be induced and must be isolated¹. Rescuers should wear protective suits such as face masks, eye shields and double gloving, during decontamination.

Antidotes

Cyanide is a rapidly lethal toxin and antidotal treatment must take place immediately in order to be effective. However, patients may benefit from receiving antidotes after some delay. In a case series antidote administered to 14 consecutive patients beginning a median 2.1 hours (15 min – 5 ½ hour) after cyanide ingestion or inhalation, and ten patient survived¹⁷. This confirms that excellent supportive care can gain additional time to treat with antidotes¹¹.

Antidotal treatment of cyanide poisoning involves three strategies which are binding of cyanide, induction of methemoglobinemia, and use of sulfur donors.

- Direct cyanide binding: Hydroxocobalamin and dicobalt edetate are in this group.
 - o Hydroxocobalamin

Hydroxocobalamin has been employed as a cyanide antidote since the early 1970s¹¹. It is a vitamin B12 precursor and with its cobalt component in its structure bind to intracellular cyanide with a greater affinity than cytochrome oxidase and forming cyanocobalamin; a stable molecule that excreted in the urine¹⁸.

Hydroxocobalamin is available as Cyanokit® (2.5 g/vial, 2 vials). Recommended initial dose is 5g intravenously over 15 minutes. Depending on the severity of poisoning it may be repeated for a total of 10g. Its pediatric dose is 70mg/kg¹¹.

Existed data suggest that hydroxocobalamin is lacking in clinically significant adverse effects; rare adverse effects included dyspnea, facial edema and urticaria¹⁸. It may cause a reddish discoloration of the skin, plasma, urine and mucous membranes¹⁷. Intravenous infusion of hydroxocobalamin has confounding effects on therapeutic measures such as total hemoglobin, carboxyhemoglobin, methemoglobin, and oxyhemoglobin, which makes the assessment of smoke inhalation victims difficult¹⁸.

In general hydroxocobalamin as first-line antidotal therapy is effective and safe in acute cyanide poisoning¹⁷.

- o Dicobalt edetate

Dicobalt edetate is a cobalt compound, whose efficacy being based upon the fact that cyanide combines with cobalt to form a relatively non-toxic complexes¹⁹. It is found as Kelo-cyanor %1,5® (300mg/20ml) ampules at National Poison Counselling Center. Recommended adult dose is 300 mg over 1 minute, followed immediately by 50 ml of 50% dextrose¹¹.

Adverse effects reported have included hypertension, tachycardia, nausea, retrosternal pain, sweating, palpebral, facial and laryngeal edema, vomiting, urticaria and/or a feeling of impending doom; which appear particularly when administered in the absence of intoxication¹⁹.

- Induction of methemoglobinemia: Amyl nitrite, sodium nitrite and 4-dimethylaminophenol are in this group.
 - o Nitrites

Nitrite-based cyanide antidotes oxidize hemoglobin to methemoglobin which provides an attractive alternative binding site for cyanide, in direct competition with the site on the cytochrome, and it formed a less toxic compound².

Amyl nitrite was the first cyanide antidote, since 1888. Its use is attractive for first aid because it's inhaled from a crushed capsule, so easy to use; however it only produces about 7% methemoglobin which is insufficient to bind a lethal dose of cyanide¹. It should be administered one capsule at a time and held in front of the patient's mouth for 15 seconds, followed by rest for 15 seconds, until intravenous access is obtained and sodium nitrite infusion is started¹¹.

Sodium nitrite administered intravenously with adjustment to maintain methemoglobin levels $\leq 40\%$ ². Its recommended adult dose is 300 mg within 3-5 minutes, for pediatric patient dose is 6 mg/kg (max 300 mg)¹. The dose is often repeated at 30 minutes if the clinical response is inadequate.

A significant adverse effect of the nitrites is hypotension, induced by the release of nitric oxide¹¹. Another important consideration is the production of methemoglobin that shifts the oxygen-hemoglobin dissociation curve to the left further hindering oxygen delivery to tissues. So nitrites are not suitable for fire victims, and those with poor cardiopulmonary reserve¹¹. Appropriate dose of sodium nitrite is adjusted ac-

ording to the patient's hemoglobin levels⁹. Nitrites should also be avoided in pregnant patients because of the oxidative stress on fetal hemoglobin¹.

There were also new researches on better and safer antidotes against cyanide poisoning. It was demonstrated in an animal study that isosorbide dinitrate may have a potential to be an antidote against cyanide poisoning²⁰.

- o 4-Dimethylaminophenol

4-Dimethylaminophenol is a potent methemoglobin inducer which is used as a choice of antidote in German and Austria with a recommended intravenous dose of 3, 25 mg/kg¹¹. Adverse effects include reticulocytosis, nephrotoxicity, and hemolysis²¹.

- Sulfur donors: Sodium thiosulfate is in this group.

Sodium thiosulfate applies a sulfur molecule to rhodanese and allows formation of thiocyanate and regeneration of the native enzyme¹¹. Thiocyanate excreted renally. Its recommended adult dose is 12.5 g by slow intravenous route and pediatric dose is 7 g/m²¹¹. Adverse effects include local skin and muscle pain at infusion site, nausea, vomiting, headache and disorientation². Its slow onset of action is a disadvantage for its use as the sole medication in antidotal therapy¹.

Cyanide Antidote Kit which has been used for decades for acute cyanide poisoning, consists of 3 medications given together for their synergistic effect: amyl nitrite, sodium nitrite, and sodium thiosulfate.

Table 1. Recommendation for antidotal treatment strategies in case of cyanide poisoning for adults

Situation	Recommended antidote regime
In case of probable cyanide intoxication	
<ul style="list-style-type: none"> • If hydroxocobalamin is available 	Hydroxocobalamin (Cyanokit®) 5 g IV over 15 min AND Sodium thiosulfate 12.5 g IV over 30 min
<ul style="list-style-type: none"> • If hydroxocobalamin is not available <ul style="list-style-type: none"> o And if there is no contraindication to nitrites 	Cyanide Antidote Kit® Amyl nitrite inhaled for 15 sec, followed by 15 sec rest until sodium nitrite infusion started AND Sodium nitrite 300 mg IV over 3-5 min AND Sodium thiosulfate 12.5 g IV over 30 min
<ul style="list-style-type: none"> • If hydroxocobalamin is not available <ul style="list-style-type: none"> o And if there is a contraindication to nitrites 	Sodium thiosulfate 12.5 g IV over 30 min
<ul style="list-style-type: none"> • If hydroxocobalamin and Cyanide Antidot Kit are not available 	4-Dimethylaminophenol 3.25 mg/kg over 1 min OR <ul style="list-style-type: none"> • And if the diagnosis is clear Dicobalt edetate (Kelocyanor %1,5®) 300 mg over 1 min
In case of questionable cyanide intoxication	
<ul style="list-style-type: none"> • If hydroxocobalamin is available 	Hydroxocobalamin (Cyanokit®) 5 g IV over 15 min AND Sodium thiosulfate 12.5 g IV over 30 min
<ul style="list-style-type: none"> • If hydroxocobalamin is not available <ul style="list-style-type: none"> o And if Cyanide Antidot Kit is available 	Sodium thiosulfate 12.5 g IV over 30 min

*Abbreviations: IV; intravenous, min; minute, g; gram

In line with the above information, recommendations regarding antidote selection in cyanide poisoning are summarized in Table 1⁹.

Conclusion

Cyanide poisoning is a rapidly lethal, serious poisoning. Clinical features are dependent on the route, duration and amount of exposure. Serum lactate levels can be used for confirmation of the diagnosis and predict the severity of poisoning. Supportive care, decontamination and adjunctive antidotal therapy are the main element of management. Recommendation for antidotal treatment strategies in case of cyanide poisoning depends on the availability of antidotes and accuracy of the diagnosis.

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