Cyanide is widely recognized as one of the most rapidly acting and lethal poisons known. It has been associated with high profile mass poisonings, homicides, and suicide attempts. \(^1\)\(^2\) It is believed to have caused more than 1 million deaths in Nazi gas chambers at Auschwitz, Buchenwald, and Majdanek. It has also been used as a chemical weapon by various governments. In 1978, it was used in a mass suicide led by Jim Jones of the People’s Temple in Guyana and resulted in 913 deaths. In 1982, an unknown terrorist adulterated Tylenol packages with cyanide in the Chicago area, resulting in 7 deaths. Public outrage over this event led to the requirement of tamper-resistant or -evident packaging for over-the-counter drugs in the US.

Cyanide and related compounds have numerous industrial uses, ranging from gold mining to health care. Cyanogenic compounds, such as amygdalin, can be found in certain plants, particularly in the seeds and pits of members of the genus *Prunus*. This includes apricot pits, cherry pits, apple seeds, and almond husks. Despite cyanide’s widespread use, relative availability, and notoriety, acute poisoning is relatively infrequent in the US. It is rarely seen by clinicians working outside of prehospital and emergency department settings.

Cyanide poisoning accounted for 220 of the 2.4 million cases of poisoning reported to the American Association of Poison Control Centers in 2005.\(^3\) This dataset is limited by the nature of voluntarily reported data and has a tendency to primarily reflect data on ingestions. An additional limitation is that cases of victims who are found dead are traditionally underreported to poison centers, which is es-

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**Role of Hydroxocobalamin in Acute Cyanide Poisoning**

Greene Shepherd and Larissa I Velez

**OBJECTIVE**: To review the recently approved cyanide antidote, hydroxocobalamin, and describe its role in therapy.

**DATA SOURCES**: Relevant publications were identified through a systematic search of PubMed using the MeSH terms and key words hydroxocobalamin and cyanide. This search was then limited to human studies published since 2000. Systematic searches were conducted through January 2008. References from identified articles were reviewed for additional pertinent human studies.

**STUDY SELECTION AND DATA EXTRACTION**: The literature search retrieved 7 studies on the safety and/or efficacy of hydroxocobalamin in humans. Four new studies were identified by the search and 3 studies were identified from the references.

**DATA SYNTHESIS**: Studies of antidote efficacy in humans are ethically and logistically difficult. A preclinical study demonstrated that intravenous doses of hydroxocobalamin 5 g are well tolerated by volunteer subjects. Hydroxocobalamin has been shown to reduce cyanide concentrations in controlled studies of nitroprusside therapy and in heavy smokers. A retrospective study of 14 acute cyanide poisonings also demonstrated hydroxocobalamin’s safety and efficacy. Two studies examining hydroxocobalamin for smoke inhalation–associated cyanide poisoning indicated a possible benefit, but they are insufficient to establish definitive criteria for use in this setting. Randomized controlled trials of hydroxocobalamin and traditional cyanide antidotes (nitrites/thiosulfate) are lacking.

**CONCLUSIONS**: Cyanide poisoning can rapidly cause death. Having an effective antidote readily available is essential for facilities that provide emergency care. In cases of cyanide ingestion, both the nitrite/thiosulfate combination and hydroxocobalamin are effective antidotes. Hydroxocobalamin offers an improved safety profile for children and pregnant women. Hydroxocobalamin also appears to have a better safety profile in the setting of cyanide poisoning in conjunction with smoke inhalation. However, current data are insufficient to recommend the empiric administration of hydroxocobalamin to all victims of smoke inhalation.

**KEY WORDS**: antidote, cyanide, hydroxocobalamin, poisoning.

pecially relevant for poisons such as cyanide, which are capable of rapid lethality.

The more common, but often underappreciated, source of cyanide toxicity is smoke inhalation, which is estimated to cause 5000–10,000 deaths annually in the US. Mortality from smoke inhalation is typically 24–31%. Historically, carbon monoxide was thought to be the primary cause of smoke inhalation–associated morbidity and mortality, but cyanide may be equally important. Cyanide gas is released as a combustion product when certain plastics and wool burn. Prospective studies in which cyanide concentrations were measured within hours of smoke exposure indicate that cyanide poisoning can contribute significantly and independently to morbidity and mortality associated with smoke inhalation.

### Cyanide’s Pathopharmacology

Cyanide is known to inhibit several enzyme systems that use iron for reduction–oxidation reactions, but its primary mechanism of toxicity is prevention of mitochondrial oxygen utilization. In the mitochondria, cyanide reversibly binds ferric iron in cytochrome oxidase a3, which inhibits oxidative phosphorylation, leading to depletion of intracellular adenosine triphosphate (Figure 1). The inability of the body to utilize oxygen for energy production causes a shift from aerobic to anaerobic metabolism, which increases lactic acid formation. Lactic acid accumulation results in a high anion gap metabolic acidosis. Because cyanide prevents the cell from using oxygen, cellular hypoxia occurs even in the presence of (normally) adequate or excessive oxygen levels in the blood. Organs with a high demand for oxygen, such as the brain and heart, are the most susceptible to cyanide poisoning.

The signs and symptoms of cyanide poisoning are very similar to those seen with other causes of tissue hypoxia (Table 1). The onset of cyanide’s toxicity is typically less than 1 minute after inhalation and a few minutes after ingestion, but can vary depending on the extent of exposure. Cyanide poisoning is initially manifested as transient hyperpnea (rapid, deep respirations) and tachycardia accompanied by headache, dizziness, and nausea/vomiting. With prolonged hypoxia, this is followed by hypoventilation, hypotension, and myocardial depression. Later manifestations of cyanide poisoning include cardiac arrhythmias, stupor, coma, and seizures, which culminate in cardiorespiratory arrest and death.

In survivors, long-term cognitive deficits and neuropsychiatric problems have been reported. These changes in regional sensitivities of the brain are thought to be due to hypoxic stress. The clinical symptoms are similar to those of carbon monoxide poisoning. The neurologic sequelae of cyanide intoxication progress over a period of weeks to months and may persist for up to a year.

Although varying values for toxic and lethal blood concentrations of cyanide are reported in the literature, many sources suggest that blood cyanide concentrations greater than 0.5 mg/L cause toxicity and that lethal concentrations typically exceed 3 mg/L. Treatment is usually required when blood cyanide concentrations exceed 1 mg/L.

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**Figure 1.** Effect of cyanide on mitochondrial metabolism. (A) Depicts normal electron transport and aerobic metabolism. (B) Depicts the effect of cyanide on this system. Cyanide binds to the iron in the cytochrome a3 complex. Oxidative phosphorylation is blocked and oxygen no longer is utilized. Cellular energy production shifts to anaerobic metabolism, which results in acidosis. Cyt = cytochrome; Cu = copper; ADP = adenosine diphosphate; ATP = adenosine triphosphate; Hb = hemoglobin.
Cyanide displays first-order kinetics during the period of initial toxicity. The volume of distribution appears to increase with higher doses. These kinetic changes probably reflect the marked intracellular sequestration of the molecule. The route of administration also plays an important role in cyanide’s distribution. Animal studies have indicated that inhaled cyanide selectively accumulates in the lung, heart, and brain, while ingestion is subject to a significant first-pass effect as evidenced by higher liver concentrations.²

**Clinical Management**

The differential diagnosis for acute cyanide poisoning is relatively small; thus, the empiric use of an antidote should be considered for patients with evidence of tissue hypoxia but lacking the typical pallor and/or cyanosis.¹²,¹⁴ In such situations, a high level of clinical suspicion should always be maintained, as the laboratory evaluation of cyanide toxicity is of limited value given cyanide’s rapid action and lethality.

Patients with suspected cyanide exposure should undergo appropriate decontamination. For patients with inhalation exposure, removal from the contaminated area and disrobing are typically sufficient decontamination. If the patient is grossly contaminated (vomitus or spilled liquid), more extensive decontamination will be required to reduce the chance of secondary contamination of healthcare workers. Gastrointestinal decontamination measures are not highly effective due to the high potency, rapid onset, and small molecular size of cyanide. However, if patients present within one hour of ingestion, it is reasonable to perform orogastric lavage and/or administer activated charcoal in an attempt to limit cyanide’s absorption.¹⁵,¹⁶

As with any critically ill patient, basic supportive care is paramount. Airway management should be addressed initially. Supplemental oxygen (100% by non-rebreather mask or endotracheal tube) is an essential part of supportive care in cyanide poisoning.¹⁷ Although supplemental oxygen will not correct the underlying problem, it is a necessary part of treatment, as decreased oxygen availability has been shown to cause up to a tenfold increase in cyanide toxicity and increased lethality in mice.¹⁸ Furthermore, oxygen may enhance the antidote’s effectiveness by competing with cyanide for cytochrome oxidase binding sites. The use of hyperbaric oxygen for cyanide toxicity and smoke inhalation is controversial, and methods for identifying cases that would clearly benefit from its use are lacking.¹ Blood pressure should be closely monitored, and isotonic crystalloids and vasopressors should be initiated as needed. However, early antidotal therapy is the definitive treatment for patients with suspected cyanide poisoning.

Empiric dosing without full knowledge of patient- or disease state–specific issues is often necessary. Antidote use is relatively straightforward in uncomplicated cases, where cyanide is the only cause of injury (eg, no trauma, polysubstance suicide attempt, smoke inhalation) and the patient lacked concurrent medical conditions or metabolic abnormalities that would modify response to cyanide or antidotes. In cases with potential complicating factors, antidote selection is less straightforward.

Currently, there are 2 different cyanide antidotes available for use in the US: a 3-drug antidote consisting of nitrates and thiosulfate, and hydroxocobalamin (Table 2).¹⁹,²⁰ The 3-drug kit has been used successfully since the 1950s. Hydroxocobalamin, which became available in the US in 2007, has been used in Europe since the 1970s.¹⁴

**NITRITE/THIOSULFATE THERAPY**

The nitrite/thiosulfate antidote kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate. The classic study for the nitrite/thiosulfate combination was published by Chen and Rose²¹ in 1952. This report is the basis for the widespread use of the 3-drug nitrite/thiosulfate combination and predated the formal Food and Drug Administration approval process. The authors administered thiosulfate, amyl nitrite, and/or sodium nitrites in various combinations to cyanide-poisoned dogs and reported the ratio of observed 50% lethal doses (LD₅₀) between untreated controls and treated animals. The combination of thiosulfate with either nitrite was superior to the administration of thiosulfate or nitrite alone. The combinations allowed survival at LD₅₀ 11 (amyl nitrite and thiosulfate) to 18 (sodium nitrite and thiosulfate) times higher than the control and 2–3 times higher than the individual components. The report continued with a summary of 24 cases of humans who had successfully responded to the antidotes. In this summary, the time to antidote administration ranged from 2 minutes to 2.5 hours. Since then, numerous case reports have validated this regimen as being effective but have also identified several important limitations, which are discussed below.¹⁴

The combination of nitrates and thiosulfate has a synergistic effect (Figure 2). Nitrates are used to induce metha-

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**Table 1. Common Signs and Symptoms of Cyanide Poisoning**¹⁹

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Altered mental status</td>
<td>Headache</td>
</tr>
<tr>
<td>Seizures and/or coma</td>
<td>Confusion</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Tachypnea and hyperpnea</td>
<td>Chest tightness</td>
</tr>
<tr>
<td>Hypertension (early)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Hypotenstion (late)</td>
<td></td>
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<tr>
<td>Cardiovascular collapse</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Plasma lactate ≥8 mmol/L</td>
<td></td>
</tr>
<tr>
<td>High venous oxygen saturation</td>
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</tbody>
</table>
moglobinemia. Cyanide appears to preferentially bind to the ferric iron of methemoglobin (metHb) rather than cytochrome a3 in the mitochondria. This displacement of cyanide away from cytochrome a3 reactivates mitochondrial electron transport, which restores aerobic metabolism. Amyl nitrite, a highly volatile liquid that comes packaged in 0.3-mL crushable glass ampuls, is designed as a temporizing measure while an intravenous line is being established. Inhaling the vapor for 30 seconds will generate approximately 5% metHb. Subsequently, sodium nitrite 300 mg (10 mL of a 3% solution) is administered intravenously, resulting in 15–20% of metHb in adults. In children, the sodium nitrite dose needs to be adjusted based on hemoglobin concentration to prevent excessive metHb formation and hemolysis. Pediatric doses of sodium nitrite range from 5.8 to 11.6 mg/kg for hemoglobin concentrations ranging from 7 to 14 g/dL.

Nitrites can cause significant adverse effects, namely, vasodilatation and hypotension. In a patient already in shock, it may not be feasible to administer these agents. Although metHb is the desired endpoint of therapy, its formation can negatively impact the condition of certain patients. Nitrites should be avoided during pregnancy due to fetal hemoglobin’s susceptibility to oxidative stress. Infants and very young children will have some residual fetal hemoglobin and reduced metHb reductase activity, which makes them more susceptible to nitrite-induced methemoglobinemia and hemolysis. In children, if an immediate hemoglobin measurement is unavailable, nitrites should be avoided, but sodium thiosulfate can be used. Nitrites are also problematic for patients with poor cardiopulmonary reserve or those with other conditions that impair oxygen-carrying capacity, including carbon monoxide poisoning.

The third component of the cyanide antidote kit is intravenous sodium thiosulfate. This agent enhances the clearance of cyanide by acting as a sulfur donor. Thiosulfate, in a reaction catalyzed by rhodanese, reversibly combines with extracellular cyanide to form thiocyanate, which can be excreted in the urine. Thiosulfate may also augment mitochondrial sulfur transferase reactions that lead to intracellular thiocyanate formation. Thiosulfate has been used as the sole treatment for victims of smoke inhalation with anecdotal reports of success, but has never been formally evaluated. The effectiveness of sodium thiosulfate as a stand-alone antidote is limited by its delayed onset of action and small volume of distribution. As short-term therapy, thiosulfate has very few adverse effects; the main reactions of concern are hypersensitivity and infusion rate–related hypotension. An indirect toxic effect of thiosulfate is thiocyanate accumulation and degradation (Fig-

<table>
<thead>
<tr>
<th>Three-Drug Antidote</th>
<th>Amyl Nitrite</th>
<th>Sodium Nitrite</th>
<th>Sodium Thiosulfate</th>
<th>Hydroxocobalamin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>induces ~5% MetHb via oxidation</td>
<td>induces ~20% MetHb via oxidation</td>
<td>combines with unbound cyanide to form thiocyanate</td>
<td>combines with unbound cyanide to form cyanocobalamin</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>crushed ampul inhaled for 30 sec, may be repeated every 5–3 min until iv access established</td>
<td>300 mg for adults; 5.8–11.6 mg/kg in children, based on Hb level</td>
<td>given iv over 20–30 min, repeat half dose if needed</td>
<td>5 g for adults; 70 mg/kg in children</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>rapid administration via inhalation; rapid onset of action</td>
<td>rapid onset of action</td>
<td>low toxicity</td>
<td>rapid onset of action; low toxicity</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>multi-part antidote less effective when used alone caution should be used when given to hypotensive or hypoxic pts. abuse potential</td>
<td>multi-part antidote less effective when used alone caution should be used when given to hypotensive or hypoxic pts. requires Hb estimation or measurement for proper dosing in children</td>
<td>multi-part antidote less effective when used alone delayed onset of action when used alone</td>
<td>skin and urine discoloration may require additional doses</td>
</tr>
<tr>
<td><strong>A WP</strong></td>
<td>$274.56 for one 3-part kit</td>
<td>$812.50 for two 2.5-g vials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AWP = average wholesale price (as of Jan 2008); FDA = Food and Drug Administration, Hb = hemoglobin, metHb = methemoglobin.*
HYDROXOCOBALAMIN

Hydroxocobalamin works by an entirely different mechanism compared with the nitrites (Figure 3). It is an endogenous vitamin B<sub>12</sub> precursor (B<sub>12a</sub>) that binds cyanide to its cobalt moiety in equimolar amounts to form cyano-
obalamin (vitamin B<sub>12</sub>).<sup>23</sup> It has a greater affinity for cyanide than cytochrome oxidase. Animal models have demonstrated that hydroxocobalamin is an effective antidiode against lethal doses of cyanide.<sup>1,14</sup>

Hydroxocobalamin is available as a lyophilized powder that forms a clear red liquid when reconstituted. It should be administered through a dedicated intravenous line, since it is known to be incompatible with several drugs commonly used in resuscitation and with the other cyanide antidiodes.<sup>19</sup> When administered for vitamin deficiencies, hydroxocobalamin is typically dosed in micrograms or milligrams. When used as a cyanide antidiode, much larger doses (grams) are required. The recommended starting dose is 5 g administered intravenously over 15 minutes, but it can be given more slowly if infusion rate-related problems develop. Additional doses of 2.5 g may be given as needed to reverse the symptoms of cyanide toxicity. For children, an initial dose of 70 mg/kg can be followed by a 50% repeat dose (35 mg/kg) if needed. Significant adverse reactions to hydroxocobalamin therapy are rare at recommended doses. However, reddening of the skin and urine, which can last for several days, will occur in most patients.<sup>24-26</sup> Allergic reactions and transient hypertension also have been rarely reported. Hydroxocobalamin, due to its red color, can interfere with several common spectrophotometric tests, including serum aspartate aminotransferase, creatinine, bilirubin, magnesium, and serum iron.<sup>14</sup> It has also been shown to interfere with tests for carboxyhemoglobin, metHb, and oxyhemoglobin, all potentially pertinent tests for victims of smoke inhalation or cyanide poisoning.<sup>27</sup>

HUMAN STUDIES WITH HYDROXOCOBALAMIN

Due to the high toxicity of cyanide and the relative rarity of poisoning cases, controlled antidote studies in humans are ethically and logistically very difficult to perform. Consequently, there are no head-to-head comparisons of the nitrite/thiosulfate combination or thiosulfate alone with hydroxocobalamin. However, we review available data on the safety and efficacy of hydroxocobalamin in the clinical setting.

In 1978, Cottrell et al.<sup>28</sup> investigated the effects of hydroxocobalamin infusions (25 mg/h) in patients receiving intravenous nitroprusside, which can cause cyanide toxicity with prolonged use, high doses, and in patients with renal impairment. In this study, the small amounts of cyanide produced by nitroprusside therapy were neutralized by a supratherapeutic dose of hydroxocobalamin. Concomitant administration of hydroxocobalamin with nitroprusside reduced the red blood cell and plasma cyanide concentrations by about 60%. If the hydroxocobalamin infusion was stopped before the nitroprusside infusion, cyanide concentrations and degree of acidosis became similar to those in the group who did not receive hydroxocobalamin. No adverse effects were reported, except transient reddening of the urine and mucous membranes. Similar results were reported in a subsequent study.<sup>29</sup>

Another study administered hydroxocobalamin 5 g intravenously to 15 adults who were heavy smokers.<sup>30</sup> All subjects had above-normal cyanide concentrations, but the concentrations were well below the threshold for clinically evident poisoning (<2 µmol/L). In these patients, hydroxocobalamin caused increases in systolic blood pressure (by 13.6%) and diastolic blood pressure (by 25.9%). Also, there was a concomitant 16.3% decrease in heart rate. These effects persisted for up to 60 minutes, during which the subjects reported no ac-
companying symptoms. Discoloration of mucous membranes, skin, and urine was noted in all who received hydroxocobalamin. The discoloration was also asymptomatic and spontaneously resolved within 48 hours. Hydroxocobalamin alone decreased blood cyanide concentrations by 59% \((p < 0.01)\) and increased urinary cyanide excretion. The urinary cyanide excretion was greater than the estimated total blood cyanide burden. The authors concluded that hydroxocobalamin may help eliminate cyanide “from other tissues than the blood.”

A more recent study evaluated the safety of high-dose hydroxocobalamin in adults.\(^\text{26}\) In this randomized, double-blind, placebo-controlled trial, dose safety and tolerability were evaluated. Hydroxocobalamin was given intravenously in 4 ascending doses of 2.5, 5, 7.5, and 10 g over 7.5–30 minutes. A total of 136 participants were enrolled, of whom 102 were randomized to receive hydroxocobalamin and 34 to receive placebo. The study was stopped prematurely after the rate of adverse reactions in the 10-g arm was deemed “not acceptable for volunteers.” The most common adverse reactions were chromaturia (seen in all pts.) and reddening of the skin (seen in almost all pts.). Other reactions included a papular/pustular rash, headache, erythema at injection site, decreased lymphocyte percentage, nausea, pruritus, chest discomfort, and dysphagia. Two allergic reactions occurred during administration of doses between 4 and 5 g. An increase in blood pressure, usually starting toward the end of the infusion and returning to normal within 4 hours, was noted. The mean systolic and diastolic blood pressure increases averaged 23 and 18 mm Hg, respectively. Heart rates also were noted to decrease from baseline. This study established that intravenous doses of 2.5 and 5 g are generally well tolerated by nonpoisoned humans. Although a reasonable number of subjects were enrolled, the vast majority of participants were of Scandinavian origin, which may limit the ability to generalize results to other ethnic groups.

Several case reports and letters to the editor have been published describing the safety and efficacy of hydroxocobalamin in humans after acute cyanide ingestions.\(^\text{14}\) Adverse effects reported in these cases were mild and are consistent with the previous published literature. In one of these cases, cyanide concentrations increased after administration of hydroxocobalamin.\(^\text{30}\) It is unclear whether this phenomenon was due to delayed absorption or redistribution, but another study’s findings support redistribution as the primary cause.\(^\text{30}\)

Borron et al.\(^\text{32}\) reported a chart review on the use of hydroxocobalamin in patients with cyanide poisoning. This study excluded patients with cyanide toxicity from smoke inhalation. Hydroxocobalamin 5–20 g was given intravenously to 14 patients (12 were suicide attempts), along with standard supportive care. Ten (71%) patients survived to discharge. All 4 who died were in cardiac and/or respiratory arrest prior to antidote administration. In 12 patients who had pretreatment cyanide concentrations, the mean was 159 \(\mu\)mol/L. Eleven patients had cyanide concentrations of 100 \(\mu\)mol/L or more (considered potentially lethal); 7 of these patients survived. The mean administration time for the antidote was 3.1 hours after the cyanide ingestion. Of note, hydroxocobalamin was the only cyanide antidote in 9 patients; the others also received thiosulfate and/or dicobalt edetate. Eight (57%) patients developed adverse reactions: chromaturia \((n = 5)\), red/pink skin discoloration \((n = 3)\), increase in heart rate \((n = 1)\), and elevated blood pressure \((n = 1)\). This study demonstrated that hydroxocobalamin could be used safely with apparent benefit in patients with acute cyanide poisoning.

In a retrospective review, the prehospital use of hydroxocobalamin for smoke inhalation was evaluated using the charts of 101 patients.\(^\text{28}\) Blood cyanide concentrations were not measured. A total of 30 patients survived; 42 died \((41.7\% \text{ survival rate for those whose status was known})\). In 29 cases, the survival outcome was not known. A total of 38 patients were in cardiac arrest when found. Of these, 21 had spontaneous recovery of circulation, 19 of whom later died in the intensive care unit. Twelve patients were hemodynamically unstable \((\text{defined by the authors as systolic blood pressure } > 0 \text{ and } < 90 \text{ mm Hg})\). Nine \((75\%)\) patients “recovered” a blood pressure about 30 minutes after treatment. Hydroxocobalamin appeared more beneficial when given to pa-

![Figure 3. Antidotal mechanism of hydroxocobalamin.](image-url)
Patients with neurologic impairment (Glasgow Coma Scale score <13). Adverse reactions noted were skin/urine discoloration (n = 5) and rash (n = 1). This study supported previous findings of hydroxocobalamin’s safety in humans. However, survival was considerably lower than the expected survival rates of 69–84% for smoke inhalation.6

Findings of this study suggest that hydroxocobalamin’s use in smoke inhalation may be beneficial for patients with neurologic impairment. Since the investigators did not correlate symptoms with cyanide concentrations, these potential benefits cannot be considered conclusive.

Borron et al.24 performed a prospective, uncontrolled, open-label study on prehospital use of hydroxocobalamin for smoke-induced cyanide poisoning. To be eligible, patients had to be older than 15 years, have soot in the mouth/nose/expectoration, and have altered neurologic status. Patients with burns to face and neck, burns that were second degree or greater involving 20% or more of the body surface area, obvious external multiple organ trauma, or those who were pregnant were excluded. Prior to antidote administration, blood samples were obtained for cyanide and carbon monoxide measurement. Hydroxocobalamin 5 g was then given intravenously over 15–30 minutes, and doses could be repeated, up to a total of 15 g. The study enrolled 69 patients, but only 63 had pre-antidote blood concentrations determined. Cyanide was present (>39 µmol/L) in 42 (67%) patients, with a median cyanide concentration of 52 µmol/L. Overall, the survival rate was 72% (n = 50). In the subset of patients with potentially lethal cyanide concentrations (≥100 µmol/L), survival was 58% (11/19). The median hydroxocobalamin dose administered in this study was 5 g. Nineteen patients had adverse reactions associated with hydroxocobalamin, the most common being chromaturia (n = 6), pink/red skin discoloration (n = 4), increased blood pressure/hypertension (n = 5), and erythema (n = 2). No allergic reactions were reported.

This study demonstrated survival among patients with potentially lethal cyanide concentrations when hydroxocobalamin was administered.24 Patients in cardiorespiratory arrest when they were discovered or those with severe neurologic deficits were less likely to respond to therapy. Although the overall survival rates were no better than those expected without an antidote, patients with milder neurologic deficits appear likely to benefit from hydroxocobalamin. Unfortunately, there were no control or alternative treatment groups, which somewhat limits the value of these findings.

Formulary Considerations

To be considered for formulary addition, a new drug should provide some advantage over existing drugs in at least one of the following areas: mechanism, safety profile, kinetics, or cost. Differences between hydroxocobalamin and the nitrite/thiosulfate combination are summarized in Table 2. Hydroxocobalamin offers an alternative mechanism to the nitrite/thiosulfate combination. In terms of safety, it offers more straightforward administration, particularly in children. This may reduce significant adverse effects. The improved safety profile is even more evident for victims of smoke inhalation. Hydroxocobalamin does not induce methemoglobinemia. This is particularly important in patients who may have concomitant toxicity from other agents that decrease oxygen-carrying capacity, the most important of which is carbon monoxide.

Kinetically, hydroxocobalamin offers a more rapid onset of action than thiosulfate, which again may be critically important in fire victims. However, additional doses may be required more frequently for hydroxocobalamin than for thiosulfate. In France, hydroxocobalamin and thiosulfate are given in combination.24 This approach has not been formally evaluated, so it is unclear what, if any, additional benefit it provides. It seems most likely to provide benefit for victims of massive cyanide ingestion where additional doses of hydroxocobalamin might be needed. The nitrite/thiosulfate combination appears to have an advantage with respect to per-unit cost (Table 2). However, given that this is an infrequently used treatment, this cost difference is likely to have little impact on a hospital’s total drug budget.

At a minimum, any facility that provides emergency care should stock enough cyanide antidote to treat one person for up to 24 hours.23 However, it is prudent to have more on hand, given the possibility of multiple patients with cyanide presenting within a narrow time frame after large fires, mass suicides, or acts of terrorism.

Summary

Cyanide poisoning by ingestion or inhalation can rapidly cause death. Having a readily available antidote is essential for facilities that provide emergency care. In cases of uncomplicated cyanide exposure, both the nitrite/thiosulfate combination and hydroxocobalamin are effective antidotes. Due to a lack of comparative studies, it is unknown whether one regimen has superior efficacy. However, hydroxocobalamin appears to offer an improved safety profile for children, pregnant women, and victims of smoke inhalation. Thus, hydroxocobalamin may be a better choice in cases in which the diagnosis of cyanide poisoning is uncertain or in cases in which the induction of metHb may be detrimental. However, current data are insufficient to routinely recommend empiric administration of hydroxocobalamin for all victims of smoke inhalation.

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Resumen de la información sobre hidroxocobalamina, antídoto aprobado recientemente, y describir su rol en el manejo de envenenamiento con cianuro.

Objetivo: Resumir la información sobre hidroxocobalamina, antídoto aprobado recientemente, y describir su rol en el manejo de envenenamiento con cianuro.

Fuentes de información. Se identificaron publicaciones relevantes a través de una búsqueda sistemática de PubMed utilizando los términos MeSH y las palabras claves hidroxocobalamina y cianuro. Esta búsqueda se limitó a estudios en humanos publicados desde el año 2000 hasta enero de 2008. Además, se revisaron las referencias de los artículos identificados para obtener estudios adicionales pertinentes en humanos.

Selección de estudios y extracción de información. La búsqueda de literatura identificó 7 estudios sobre la eficacia o seguridad de hidroxocobalamina en envenenamiento agudo con cianuro. Estos estudios incluyeron la evaluación de la eficacia y seguridad de la hidroxocobalamina en el tratamiento de envenenamientos con cianuro en humanos. Los estudios se clasificaron en función de su diseño y metodología, y se seleccionaron aquellos que proporcionaron datos relevantes para la evaluación de la eficacia y seguridad de la hidroxocobalamina.

Resultados. Los estudios seleccionados demostraron la eficacia y seguridad de la hidroxocobalamina en el tratamiento de envenenamientos con cianuro en humanos. En general, los estudios mostraron una reducción significativa de los síntomas y signos de envenenamiento con cianuro después de la administración intravenosa de hidroxocobalamina.

Síntesis. Los estudios de la eficacia del antídoto en humanos son ética y logisticamente difíciles. Un estudio preclínico demostró que una dosis de 5 gramos intravenosos de hidroxocobalamina son bien toleradas por sujetos voluntarios. Se ha demostrado que la hidroxocobalamina reduce las concentraciones de cianuro en estudios controlados con nitroprusside y en fumadores fuertes. Un estudio retrospectivo de 14 envenenamientos agudos con cianuro también demostró la seguridad y eficacia de hidroxocobalamina. Dos estudios que evaluaban hidroxocobalamina en inhalación de humo asociada a envenenamiento con cianuro indicaron un posible beneficio, pero no hay suficiente información para establecer
criterios definitivos para utilizar hidroxocobalamina en este escenario. Se necesitan estudios aleatorios controlados de hidroxocobalamina y los antídotos tradicionales (nitritos/tiosulfato).

CONCLUSIONES: El envenenamiento con cianuro puede causar la muerte rápidamente. Es esencial tener un antídoto efectivo disponible en las instalaciones que proveen cuidado de emergencia. En casos de ingesta de cianuro, la combinación de nitrito- tiosulfato o hidroxocobalamina son antídotos efectivos. La hidroxocobalamina ofrece una alternativa más segura en caso de niños y mujeres embarazadas. En el caso de envenenamiento con cianuro unido a la inhalación de humo, la hidroxocobalamina también parece ofrecer un mejor perfil de seguridad. Sin embargo, la información disponible al momento es insuficiente para recomendar la administración empírica de hidroxocobalamina a víctimas de inhalación de humo.

Traducido por Annette Pérez

Place de l’Hydroxocobalamine dans l’Intoxication Cyanhydrique Aiguë
G Shepherd et LJ Velez

RÉSUMÉ
OBJECTIFS: Faire le point sur l’antidote des cyanures récemment autorisé, l’hydroxocobalamine, et décrire son rôle en thérapeutique.


Traduit par Michel Le Duff

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