Sodium Thiosulfate or Hydroxocobalamin for the Empiric Treatment of Cyanide Poisoning?

Alan H. Hall, MD
Richard Dart, MD, PhD
Gregory Bogdan, PhD

From the Toxicology Consulting and Medical Translating Services, Inc., Elk Mountain, WY (Hall); the Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO (Dart, Bogdan); and the Departments of Preventive Medicine and Biometrics (Hall), Surgery [Emergency Medicine] (Dart), and Pharmaceutical Sciences (Bogdan), the University of Colorado Health Sciences Center, Denver, CO.

Cyanide poisoning must be seriously considered in victims of smoke inhalation from enclosed space fires; it is also a credible terrorism threat agent. The treatment of cyanide poisoning is empiric because laboratory confirmation can take hours or days. Empiric treatment requires a safe and effective antidote that can be rapidly administered by either out-of-hospital or emergency department personnel. Among several cyanide antidotes available, sodium thiosulfate and hydroxocobalamin have been proposed for use in these circumstances. The evidence available to assess either sodium thiosulfate or hydroxocobalamin is incomplete. According to recent safety and efficacy studies in animals and human safety and uncontrolled efficacy studies, hydroxocobalamin seems to be an appropriate antidote for empiric treatment of smoke inhalation and other suspected cyanide poisoning victims in the out-of-hospital setting. Sodium thiosulfate can also be administered in the out-of-hospital setting. The efficacy of sodium thiosulfate is based on individual case studies, and there are contradictory conclusions about efficacy in animal models. The onset of antidotal action of sodium thiosulfate may be too slow for it to be the only cyanide antidote for emergency use. Hydroxocobalamin is being developed for potential introduction in the United States and may represent a new option for emergency personnel in cases of suspected or confirmed cyanide poisoning in the out-of-hospital setting. [Ann Emerg Med. 2006;xx:xxx.]

INTRODUCTION
Cyanide has been used as an agent for suicide, homicide, chemical warfare, and genocide and can contribute to death of victims of smoke inhalation in enclosed space fires.1-4 In the United States, smoke inhalation causes as many as 10,000 fatalities each year.5 Of US annual burn fatalities, 60% to 80% are likely due to smoke inhalation.6 Fire smoke contains a complex mixture of gases that contribute to smoke inhalation-associated death, including hydrogen cyanide that is released from natural and synthetic materials on combustion.1,4 Cyanide and cyanogenic compounds are also potential weapons of terrorism.7,8 Because cyanide can be released from both synthetic and natural materials, terrorist acts with explosives or incendiaries, resulting in enclosed space fires, could result in poisoning, even if cyanide or cyanogenic compounds are not used.

Cyanide reacts with high affinity with metals such as ferric iron (Fe3+) and cobalt and binds to numerous critical enzyme systems in the body. Cyanide inhibits oxidative phosphorylation and causes central nervous system and cardiovascular dysfunction because of cellular hypoxia, primarily by binding to and inactivating the enzyme cytochrome oxidase (cytochrome a3).5,9

Cyanide poisoning requires immediate and aggressive treatment. The emergency diagnosis is usually difficult because there are no pathognomonic symptoms or signs,10 and laboratory confirmation of cyanide poisoning takes hours to days to obtain. A confirmed diagnosis of cyanide poisoning is not possible in out-of-hospital emergency situations. Therefore, the decision to administer specific cyanide antidotes must be made on clinical characteristics. These can include hypotension, altered mental status, elevated plasma lactate concentrations (≥10 mmol/L), and relatively normal oxygen saturation. In smoke inhalation victims, the presence of soot in the mouth and nose, with concurrent altered mental status and hypotension, suggests the possibility of cyanide poisoning.5

Because of diagnostic uncertainty, a cyanide antidote may be administered to patients who may not be poisoned. A favorable risk:benefit ratio is thus highly desirable.11-15 There are 4 antidotes used in various countries for treatment of cyanide poisoning: the Cyanide Antidote Kit (amyl nitrite, sodium
Efficacy of Hydroxocobalamin

The effectiveness of hydroxocobalamin as a cyanide antidote was first demonstrated in 1952. The mechanism of action is direct binding to cyanide to form nontoxic cyanocobalamin (vitamin B₁₂₇) that is excreted in the urine. In an in vitro study using human fibroblasts incubated in a cyanide solution, addition of hydroxocobalamin resulted in a 75% decrease in intracellular cyanide concentrations and formation of intracellular cyanocobalamin, indicating that hydroxocobalamin penetrates cells and can act intracellularly.

Animal Studies

Hydroxocobalamin crosses the blood-brain barrier and enters the cerebrospinal fluid in experimental animals. It has been tested as a cyanide antidote in animal models using mice, rabbits, guinea pigs, dogs, and baboons. The majority of these studies demonstrated antidotal efficacy of hydroxocobalamin even if administered after cyanide. No animal study compared hydroxocobalamin and sodium thiosulfate by using the same experimental protocol.

The efficacy of hydroxocobalamin was compared to saline solution vehicle for the treatment of dogs administered potassium cyanide (0.4 mg/kg per minute, intravenously). In vehicle-treated animals, the overall mortality rate was 82% (14/17), and death occurred within 4 hours to 4 days. In contrast, 79% (15/19) and 100% (18/18) of animals treated with hydroxocobalamin 75 mg/kg or 150 mg/kg, respectively, survived through 14 days after poisoning, with no neurologic or other sequelae and no significant effects on clinical chemistry or hematology tests. Administration of hydroxocobalamin was associated with beneficial increases in blood pressure beginning 1 to 3 minutes after initiation of infusion. The hydroxocobalamin doses used were designed to mimic recommended doses (5 to 10 g) administered to humans.

Human Studies, Case Series, and Reports

In humans, the published efficacy data for hydroxocobalamin consist of 1 prospective and 1 retrospective study in victims of smoke inhalation, as well as case reports and case series. Preclinical studies in heavily smoking human volunteers showed clearing of the small amounts of cyanide (<2 μmol/L) detectable in the blood of heavy smokers.

A prospective open-label noncomparative trial in victims of enclosed space fire-smoke inhalation (defined as extrication from an enclosed space fire scene; soot in the nose, mouth, or throat; and some degree of neurologic impairment) was performed in Paris from 1989 to 1994. Results have been published in abstract form. Of 69 patients, 37 were comatose and 14 were initially in cardiopulmonary arrest (apneic and pulseless). In addition to standard resuscitation measures, hydroxocobalamin was administered in the out-of-hospital setting (5 to 15 g intravenously). The survival rate was 72% (50/69). There were no neuropsychiatric sequelae in the majority (41/50) of the survivors (82%). The main causes of...
death were infectious complications (unrelated to cyanide poisoning) and decerebration.

Fortin et al\textsuperscript{41} retrospectively reported effects of hydroxocobalamin in 101 smoke inhalation victims. Among 72 patients for whom survival status was known, survival rate was 41.7% after administration of hydroxocobalamin. Of the 38 patients found in cardiac arrest, 21 had a return of spontaneous circulation during out-of-hospital care. Twelve patients were initially hemodynamically unstable (systolic blood pressure 0 to ≤90 mm Hg), and 9 recovered systolic blood pressure approximately 30 minutes after the start of hydroxocobalamin infusion. Those with significant neurologic impairment had little improvement after hydroxocobalamin administration, as assessed by Glasgow Coma Scale scores.

Survival of severe acute cyanide poisoning from sources other than smoke inhalation after administration of hydroxocobalamin alone has been documented.\textsuperscript{43-46} In a case series, 9 adult patients were poisoned by ingestion of cyanide salts (n=7), ingestion of anacintrile (n=1), and exposure to cyanogen bromide gas (n=1).\textsuperscript{43} All received hydroxocobalamin (average dose 8.1 g). Five of the 9 patients were comatose, and 6 had a systolic blood pressure less than 90 mm Hg. Administration of hydroxocobalamin was associated with improved blood pressure in patients presenting with hypotensive shock. Six patients survived, and 3 patients who were in cardiac arrest ultimately died. All 3 patients who died were admitted several hours after the onset of the poisoning, when neurologic impairment seemed irreversible.

Espinoza et al\textsuperscript{47} reported 8 pediatric patients (aged 8 to 11 years) with acute cyanide poisoning from ingestion of improperly prepared bitter cassava (\textit{Manihot esculenta}) in Venezuela. These children presented to the hospital with vomiting, excessive weakness, respiratory failure, bradycardia, hypotension, and cardiovascular collapse. Because of limited drug supply, only the 4 most acutely ill children were treated with sodium nitrite; the remaining 4 children were each treated with 500 mg of hydroxocobalamin. Both groups of children improved within a few minutes, remained asymptomatic thereafter, and were discharged the following day, with normal neurologic assessment results.

Hydroxocobalamin became available in France on an investigational use basis in about 1970 as the Anphar-Rolland trousse anticyanure containing 4 g of lypophilized hydroxocobalamin to be reconstituted in 8 g of 10% sodium thiosulfate solution stabilized with sodium sulfite. Between 1970 and 1984, 10 patients with acute cyanide poisoning treated with the trousse anticyanure were reported, as well as 1 patient treated with 200 mg of intravenous hydroxocobalamin without sodium thiosulfate.\textsuperscript{48-55} In only 2 cases was the hydroxocobalamin/sodium thiosulfate antidote combination the \textit{only} cyanide antidote administered.\textsuperscript{52,54}

**SAFETY OF HYDROXOCOBALAMIN**

In humans, a transient reddish-brown discoloration of the skin, mucous membranes, and urine occurs from the color of the medication itself. The discoloration clears during several days in poisoned patients administered an antidotal dose\textsuperscript{14} and appears to be harmless. In burn patients, discoloration of the skin and exudates can complicate the subsequent evaluation of lesion depth if this is not done before hydroxocobalamin administration.\textsuperscript{56}

In the serum, the peak light absorption of hydroxocobalamin at 325, 364, 525, and 564.5 nm can interfere with colorimetric blood chemistry analyses for liver enzymes, bilirubin, creatinine, creatine kinase, phosphorus, glucose, magnesium, and iron, which are autoanalyzer-dependent. Either falsely high or low results may be obtained, but none appear to be of major clinical significance.\textsuperscript{57-60}

After chronic administration, rare cases of anaphylaxis, anaphylactoid reactions (including bronchospasm and oropharyngeal angioedema), pruritus, or urticaria have been reported in patients receiving low-dose hydroxocobalamin (1 to 10 mg intramuscularly per month) for vitamin B\textsubscript{12} deficiency or other indications.\textsuperscript{61-67} One case of transient facial acne\textsuperscript{49} and 1 case of urticaria and Quinke’s edema\textsuperscript{50} have been reported in patients receiving antidotal doses. Both patients were administered an older formulation of 4 g of lyophilized hydroxocobalamin dissolved in 10% sodium thiosulfate solution stabilized with sodium sulfite, and dicobalt-EDTA was also administered. The current hydroxocobalamin formulation available in France contains lypophilized hydroxocobalamin alone.

In normal human volunteers administered 5 g of hydroxocobalamin intravenously during 20 minutes, mild, transient, self-limited hypertension (mean increase of 13.6% systolic and 25.9% diastolic blood pressures) accompanied by reflex bradycardia (mean decrease of 16.3% in pulse rate) was noted.\textsuperscript{42} There were no changes on ECG and no clinically significant abnormalities of CBC counts, liver and kidney function test results, serum electrolyte levels, prothrombin and partial thromboplastin times, or blood glucose levels. All subjects remained asymptomatic and all findings returned to baseline without treatment.

A randomized, double-blind, placebo-controlled, ascending dose study was conducted to evaluate the safety of hydroxocobalamin in healthy volunteers.\textsuperscript{68} One hundred thirty-six volunteers were randomized to receive either hydroxocobalamin (2.5 g, 5 g, 7.5 g, 10 g) or placebo by intravenous infusion during 7.5 to 30 minutes. The most common hydroxocobalamin-related effects were chromaturia and reddening of the skin. Other common adverse events were pustular or papular rash, headache, erythema at the injection site, decrease in lymphocyte percentage, and chest pressure. Hydroxocobalamin was associated with a modest increase in blood pressure that was self-limiting. The clinical relevance of the increase in blood pressure in this and other studies is unclear but may be desirable in cyanide poisoning because it avoids the hypotension associated with nitrite-containing cyanide antidotes.\textsuperscript{12} Two allergic reactions occurred within minutes of

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initiation of infusion in volunteers assigned to receive the 5-g and 10-g doses, respectively, and were successfully managed with dexamethasone, dimethindene maleate, or both. This finding is similar to isolated reports of allergic reactions to hydroxocobalamin during chronic intramuscular administration for vitamin B12 deficiency. More severe manifestations, including wheezing, hypotension, or stridor, did not occur. No cases of allergic reactions have been reported after administration to 170 acutely poisoned patients.

Breton et al reported 2 children who experienced smoke inhalation and presented comatose, covered in soot, but without burns. Both patients received hydroxocobalamin in the out-of-hospital setting. The 11-month-old child was cyanotic but not acidic. The 4 1/2-year-old child was not cyanotic and had an initial pH of 7.21; however, the arterial blood gas values suggested a respiratory rather than a lactic acidosis. Neither had plasma lactate concentrations suggestive of a significant cyanide poisoning component to their smoke inhalation (plasma lactate concentrations <10.0 mmol/L). Both children developed chronic respiratory sequelae. Although neither child appeared to have significant cyanide poisoning, out-of-hospital administration of the recommended hydroxocobalamin dose was not associated with any adverse effects.

**EFFICACY OF SODIUM THIOSULFATE**

Sodium thiosulfate removes cyanide from the blood through the action of the enzyme rhodanese. Sodium thiosulfate has limited distribution into the brain, an organ highly susceptible to the effects of cyanide-induced histotoxic anoxia, and has limited penetration into the mitochondria, where the endogenous cyanide-detoxifying enzyme rhodanese is located. No clinical trials of sodium thiosulfate are available, and efficacy has been extrapolated from case studies and series of acute cyanide poisoning.

**Animal Studies**

Most experimental animal studies have compared sodium thiosulfate alone to its combination with other antidotes, most often sodium nitrite or hydroxocobalamin. In dog studies with a continuous infusion of hydrocyanic acid at 0.1 mg/kg per minute, Hug and Marenzi reported that both methylene blue and sodium nitrite were clearly more efficacious than sodium thiosulfate alone.

Kinetic studies have shown that administration of sodium thiosulfate accelerates by more than 3 times the conversion of cyanide to much less toxic thiocyanate by the endogenous rhodanese enzyme. However, sodium thiosulfate has generally been thought to have only a preventive action and not a curative action (eg, it has to be administered before the onset of cyanide poisoning symptoms and signs to be efficacious). In studies of rabbits administered potassium cyanide by gastric instillation, Hug and Marenzi found that 7 of 10 animals died despite administration of 1 g of sodium thiosulfate intravenously after cyanide administration. They also noted that sodium thiosulfate, which was practically nontoxic in normal animals, caused shock and decreased the time to cardiac arrest and death when subsequently administered to the poisoned animals. These effects were also noted when sodium thiosulfate was mixed with sodium nitrite and administered. The effects were exacerbated when the sodium thiosulfate dose was increased. The best results were obtained when sodium nitrite was administered first, followed by sodium thiosulfate. Hug concluded that sodium thiosulfate “... requires a certain latent period to exert its antitodal action ... it has a preventive [eg, must be administered prophylactically before the cyanide] but not a curative [eg, efficacious after poisoning symptoms develop] effect on cyanide poisoning.”

In a sodium cyanide continuous infusion dog model, sodium thiosulfate was not effective if administered any later in the poisoning than the beginning of the phase of primary apnea. Sodium nitrite with sodium thiosulfate, hydroxocobalamin with sodium thiosulfate, 4-DMAP, and dicobalt-EDTA were all effective at later phases of the poisoning.

In a recent study, rats were administered potassium cyanide intraperitoneally, followed 6 to 16 minutes later (when blood cyanide concentrations were expected to peak) by intraperitoneal sodium thiosulfate or normal saline solution at 225 mg/kg. In the sodium thiosulfate–treated animals, there were significantly lower arterial blood cyanide concentrations, arterial and venous lactate concentrations, and venous PO2, indicating curative efficacy for improving these cyanide toxicity markers. The authors observed that caution should be used in extrapolating these results to humans. The intraperitoneal route is an unlikely route of cyanide exposure and would not be used for sodium thiosulfate administration in humans. The dose used was somewhat higher than that recommended in humans (approximately 179 mg/kg), and survival or death was not an endpoint.

**Human Studies, Case Series, and Case Reports**

No clinical trials in humans that assess the efficacy of sodium thiosulfate alone were found. Case reports have associated sodium thiosulfate with survival. Chin and Calderon described a 19-year-old woman who drank an unknown substance containing a “high concentration” of cyanide. Coma, hypotension, and dilated pupils were noted. Initial arterial blood gases showed a severe acidosis, with a pH of 7.01, and the plasma lactate level was 10.0 mmol/L. Initial treatment with 12.5 g of sodium thiosulfate intravenously was followed by improvement of the pH to 7.17. The patient survived with sodium nitrite and further sodium thiosulfate plus supportive measures, but sequelae of short-term memory difficulties and bradykinesia developed.

Persson described 5 cases of cyanide poisoning, 4 treated with sodium thiosulfate alone and 1 treated initially with sodium thiosulfate followed by dicobalt-EDTA. For some of these patients, blood cyanide concentrations were reported. Potentially toxic concentrations of cyanide are 1 mg/L (39 μmol/L), and potentially lethal concentrations are
Twin brothers aged 2 1/2 years were found unconscious during an enclosed space fire. Both were severely acidic on presentation. Carbon monoxide concentrations were not significantly elevated. Treatment with oxygen, hyperbaric oxygen, and approximately 400 mg/kg of sodium thiosulfate was followed by recovery without sequelae. Blood cyanide concentrations were 1.15 mg/L and 1.1 mg/L.19

A 28-year-old man ingested an unknown amount of a cyanide solution. On presentation, he was talkative, anxious, and hyperventilating. Sodium thiosulfate, 15 g, was administered by slow intravenous infusion. This patient never lost consciousness but became calm and mentally clear, and the mild acidosis resolved. The blood cyanide concentration was 9.9 mg/L.19 This cyanide concentration is inconsistent with the clinical presentation and course.

A 32-year-old man was deeply comatose and slightly cyanotic after ingesting an unknown amount of a potassium cyanide solution. There was improvement 30 minutes after administration of oxygen and 8 g of sodium thiosulfate. Dicobalt-EDTA was then administered, resulting in return of normal consciousness. The blood cyanide concentration was 3.7 mg/L.19

A 54-year-old man was comatose and in respiratory arrest after ingesting 3 g of potassium cyanide. Metabolic acidosis was present (pH 7.31). An initial dose of 12 g of sodium thiosulfate was administered, followed by an additional 3-g dose. Spontaneous respiration resumed 30 minutes later, and he was alert at 6 hours after admission. There were no sequelae. The blood cyanide concentration was 0.26 mg/L.19

Of 4 previously published cases reviewed by Perrson,19 3 involved cyanide toxicity from infusion of sodium nitroprusside, which improved after administration of sodium thiosulfate. The fourth was a 30-year-old man who ingested an unknown amount of a cyanide-containing insecticide and was found comatose, apneic, and cyanotic 30 minutes later. Supportive measures and administration of sodium thiosulfate (dose not specified) was followed by return of consciousness, although persistent neurologic symptoms developed.

A 31-year-old male Japanese patient was found in bed comatose and having seizures after ingesting potassium cyanide.76 The patient had severe metabolic acidosis, an elevated central venous PO2, and normal oxygen saturation level, consistent with cyanide poisoning. Three pearls of amyl nitrite were administered, followed by 10 g sodium thiosulfate. The patient recovered during the following 30 minutes. Cyanide concentration in stored plasma was found to be approximately 1.2 mg/L when measured 6 months later.76

Two Malaysian children developed acute cassava poisoning after eating "tapioca" cake (M utilissima).77 Both had vomiting, drowsiness, and weakness. The 2 1/2-year-old boy also had reactive mydriasis, and the 1 1/2-year-old girl had dyspnea and cyanosis. Potential metabolic acidosis was reflected as a decreased alkali reserve (7.2 mmol/L) in both children. Both recovered with supportive care and intravenous infusion of 50 mL of 25% sodium thiosulfate and made full recoveries.

One of 7 patients exposed to hydrogen cyanide by inhalation in a chemical trading company office, a 19-year-old woman was discovered unconscious and hypotensive (blood pressure 77/65 mm Hg), with severe metabolic acidosis.78 The patient received amyl nitrite, and sodium thiosulfate 12.5 g was administered intravenously. The patient had repeated seizures, requiring anticonvulsant therapy. She was extubated 15 hours after admission. At 1-year follow-up, complaints of mild impairment of recent memory and concentration ability were confirmed by neuropsychological testing.

A 23-year-old German man attempted suicide by ingesting 1,500 mg of potassium cyanide.20 Six hours after hospital admission, his blood cyanide level was 6 mg/L. Supportive treatments, administration of supplemental oxygen, correction of metabolic acidosis, and administration of 1 g of sodium thiosulfate per hour for 24 hours were associated with survival.

SAFETY OF SODIUM THIOSULFATE

Dogs administered sodium thiosulfate at 3,000 mg/kg intravenously developed metabolic acidosis, hypoxemia, hypernatremia, ECG abnormalities, and changes in blood pressure.19 Dogs and rabbits administered sodium thiosulfate at 500 to 4,000 mg/kg intravenously developed hypotension.31 For comparison, the recommended adult dose of sodium thiosulfate from the Cyanide Antidote kit is 12.5 g, or about 179 mg/kg for a 70-kg person.

In normal volunteers administered 4 g of hydroxocobalamin plus 12.5 g of sodium thiosulfate intravenously, nausea, retching, vomiting, and injection site pain, irritation, and a burning sensation were observed.42,79 When sodium thiosulfate was removed from the study protocol, these effects were no longer observed, suggesting that they were due to sodium thiosulfate. In another normal volunteer study of sodium thiosulfate infusion alone, nausea and vomiting were also observed.80

CONCLUSION

The treatment of suspected cyanide poisoning presents a dilemma for first-response emergency personnel. It is important to initiate treatment as soon as possible, but some available antidotes have undesirable safety profiles and cannot be administered empirically in an out-of-hospital setting.

The evidence available to assess the 2 cyanide antidotes that can be used empirically, sodium thiosulfate or hydroxocobalamin, is incomplete. Some practitioners in the United States have used sodium thiosulfate, but there are no clinical trials to assess efficacy. In France and other countries, hydroxocobalamin is used for empiric treatment, and there are retrospective and prospective clinical studies. Because of ethical considerations, prospective, controlled clinical trial efficacy data in humans are not available for either agent, and there are no animal or human comparative studies.
Based on recent safety and efficacy studies in animals, safety studies in healthy volunteers, and uncontrolled efficacy studies in humans, hydroxocobalamin seems to be an appropriate antidote for empiric treatment of smoke inhalation and other suspected cyanide poisoning for victims in the out-of-hospital setting. It is not associated with life-threatening hypotension or methemoglobinemia found with nitrite-containing cyanide antidotes and can be administered in cases of suspected cyanide poisoning and when concurrent carbon monoxide poisoning occurs. Sodium thiosulfate can also be administered in the out-of-hospital setting. The efficacy of sodium thiosulfate is based on individual case studies, and there are contradictory conclusions about sodium thiosulfate efficacy in animal models. The onset of antidotal action of sodium thiosulfate may be too slow for it to be the only cyanide antidote for emergency use. Because there is a concern of chemical interactions when these 2 cyanide antidotes are administered simultaneously, they should not be administered in the same intravenous line.

Hydroxocobalamin is currently provided in the United States only in a dilute formulation that is not practical for use in cyanide poisoning. A more appropriate formulation is being developed for introduction in the United States. If this drug is approved, emergency physicians will have a new option for empiric treatment of cyanide poisoning in the out-of-hospital setting.

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Address for reprints: Richard Hart, MD, PhD, Rocky Mountain Poison and Drug Center, 770 Bannock Street, MC 0180, Denver, CO 80204.

Address for correspondence: Alan H. Hall, MD, TCMTS, Inc., PO Box 184, Mile 5.0 Pass Creek Road, Elk Mountain, WY 82324; 307-348-7371, fax 307-348-7372; E-mail ahalltoxic@msn.com.

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