**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

Eric Lavonas, MD and David Lobel, MD

**Date Submitted for review:**

January 22, 2010

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**Clinical question.**

**ALS-SC-073-07B**

**Primary question:**

In adult cardiac arrest (prehospital or in-hospital) due to Cyanide toxicity (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival)?

**Secondary question:**

In adults with severe cardiovascular toxicity (prehospital or in-hospital) due to Cyanide toxicity (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival)?

**Interventions studied:** The search found three antidotes that remain available for human use: hydroxocobalamin, sodium nitrite, and sodium thiosulfate. Agents that have been long-abandoned for human use, e.g. DMAP, were not considered.

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**Is this question addressing an intervention/therapy, prognosis or diagnosis?**

Therapy

**State if this is a proposed new topic or revision of existing worksheet:** New topic

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**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No (see below)

Denver Health Hospital Authority (employer of EL), has performed industry-funded research related to hydroxocobalamin therapy for cyanide poisoning. EL did not participate in this work, which was completed before he arrived.

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**Search strategy (including electronic databases searched).**

MEDLINE (via OVID): Cyanides (MeSH) /ae (adverse effects), /po (poisoning), /th (therapy), or /to (toxicity), AND [hydroxocobalamin (MeSH) OR sodium nitrite (MeSH) OR sodium thiosulfate (keyword) OR thiosulfates (MeSH) OR sodium nitrite (MeSH) OR cyanide antidote kit (keyword)] (208 records)

EMBASE: “Cyanide” (as keyword)

Cochrane CENTRAL and DARE: “Cyanide” (as keyword)

ECC EndNote X Master Library: “Cyanide” (as keyword)

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**State inclusion and exclusion criteria**

Inclusion criteria: Human clinical trials, or human observational cohort studies of hydroxocobalamin, sodium nitrite, sodium thiosulfate, or any combination thereof, for the treatment of cyanide poisoning

Exclusion criteria:

1. Animal studies
2. Studies in non-poisoned human volunteers (although not used for efficacy, these studies were cited for their safety information).
3. Single patient case reports
4. Studies of patients without life-threatening cardiovascular toxicity
5. Reports published in abstract form only

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**Number of articles/sources meeting criteria for further review:**

808 unique articles were identified by the literature search in February, 2009. After manual review, 14 reports met inclusion criteria

A supplemental search (MEDLINE only) was conducted on December 20, 2009, covering publication years 2008 – 2009 only. 8 additional articles were found, none of which met inclusion criteria.

One additional article (Espinoza, 1992, 65) was located only in the bibliography of a review article (Geller, 2006, 2146).
## Summary of evidence

### Evidence Supporting Primary Clinical Question

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- **Borron, 2007, 794 (HC; A,B)**
- **Fortin, 2006, 37 (HC; A,C)**
- **Baud, 1991, 1761 (HC + ST; A,B,C)**

### Evidence Supporting Secondary Clinical Question

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- **Borron, 2007, 794 (HC; C,D)**
- **Borron, 2007, 551 (HC; A,B,C,D)**
- **Espinoza, 1992, 65 (HC and N+ST; B,C,D)**
- **Fortin, 2006, 37 (HC; C)**
- **Baud, 1991, 1761 (HC + ST; B,C)**
- **Chen, 1952, 113 (N+ST; B,C)**
- **Kirk, 1993, 1413 (N+ST; B)**
- **Houeto, 1995, 605 (HC; E)**
- **Pontal, 1982, 90 (HC+ST; B)**

**Level of evidence**

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- **Italics** = Animal studies

**HC** = Hydroxocobalamin; **N** = Nitrites (sodium nitrite +/- amyl nitrite); **ST** = Sodium thiosulfate
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Cyanide poisoning occurs as a result of smoke inhalation, industrial accidents, ingestion of cyanogenic plant and chemical compounds, and prolonged therapy with sodium thiosulfate. Cyanide poisoning can cause profound hypotension, severe metabolic acidosis, tachy- and bradycardiac rhythms, myocardial infarction, central apnea, seizures, and death due to cardiovascular collapse. (Baud, 1991, 1761)

Three antidotal strategies are currently used worldwide: nitrite therapy (intravenous sodium nitrite, with or without inhaled amyl nitrite), sodium thiosulfate administration, and hydroxocobalamin administration. Although a multitude of other therapeutic options have been explored, they have either been abandoned as unnecessarily toxic (e.g. cobaltous chloride, dicobalt EDTA, DMAP), or never adopted for human antidotal use (e.g. alphaketoglutarate, chlorpromazine, stroma-free hemoglobin, transfusion of red blood cells loaded with thiosulfate and rhodanese). We did not consider these agents in the current review. Because oxygen administration is part of standard therapy (i.e. per algorithm) in treatment of severely ill patients, oxygen was not specifically studied in this review.

Although sodium nitrite may have multiple mechanisms of action, it is appropriate to consider the cyanide antidotes in two classes. Sodium thiosulfate is a sulfur donor: sulfane sulfur from thiosulfate combines with cyanide to produce a minimally toxic metabolite, thiocyanate. Hydroxocobalamin and nitrates (sodium nitrite and/or amyl nitrite) serve as cyanide scavengers. Hydroxocobalamin and nitrates form cyanocobalamin. Nitrates produce cyanide scavenging indirectly by oxidizing hemoglobin to methemoglobin, which directly complexes with cyanide to form cyanomethemoglobin. (Holmes, 1982, 182) Nitrates may have other important mechanisms of antidotal action, such as vasodilation. (Holmes, 1982, 182; Way, 1984, 451)

Although we did not formally review the animal literature for this worksheet, it is relevant to note that the treatment of cyanide poisoning has been studied extensively, using many different animal models. Although there are some discrepancies based on pretreatment vs. post-treatment models, interspecies’ differences, and differences in the type of supportive care administered, the literature consistently shows that all three strategies (sodium thiosulfate, hydroxocobalamin, and sodium nitrite) are more effective than placebo. When compared head-to-head, combination therapies of a sulfur donor and a cyanide scavenger (nitrates + thiosulfate; hydroxocobalamin + thiosulfate) outperform single-agent strategies. To our knowledge, only one published full-length manuscript (Bebarta, 2009, epub) directly compares the nitrite + thiosulfate and hydroxocobalamin + thiosulfate strategies. In this well-conducted swine rescue treatment model, no significant advantage was shown for either strategy.

Our search found no human clinical trials or prospective studies comparing various treatment strategies.

The use of hydroxocobalamin monotherapy is supported by 5 LOE4 studies, all of fair to poor quality (Borron, 2007, 794; Borron, 2007, 551; Fortin, 2006, 37; Houeto, 1995, 605; Espinoza, 1992, 65). These studies were a mixture of prospective observational, retrospective observational, and natural experiment design. None were clinical trials.

The use of hydroxocobalamin plus sodium thiosulfate is supported by 2 LOE 4 studies (Baud, 1991, 1761; Pontal, 1982, 90) of fair to poor quality. Study designs were observational, without comparison groups or controls.

The use of sodium nitrite plus sodium thiosulfate is supported by 3 LOE 4 studies (Kirk 1993, 1413; Chen, 1952, 113; Espinoza, 1992, 65) of fair to poor quality. Study designs were retrospective observational and natural experiment. One additional LOE 4 study of poor methodologic quality found no benefit, but was underpowered to do so. (Yen, 1995, 524)

Only one human study compared outcomes with different antidotes in a similar patient population. (Espinoza, 1992, 65) In this small report involving 8 children poisoned in the same incident, all survived (4 after receiving with sodium nitrite + sodium thiosulfate and 4 after receiving hydroxocobalamin).

Because comparative efficacy studies are incomplete, safety data are particularly important in this setting.

Nitrite therapy deliberately induces methemoglobin formation. Although the standard dose is calculated to produce 20% methemoglobinemia, the actual amount of methemoglobin generated is generally less. (Kirk, 1993, 1413). Nitrate therapy causes hypotension; in non-poisoned volunteers given 4 mg/kg intravenous sodium nitrite, median systolic blood pressure fell almost 20 mmHg, and all but one patient experienced orthostatic symptoms. (Kiese, 1969, 97). Although not reported in the setting of cyanide poisoning, nitrite therapy can cause hemolysis in glucose-6-phosphate dehydrogenase-deficient patients. One pediatric death due to sodium nitrite has been reported. (Berlin, 1976, 793)
Hydroxocobalamin causes transient hypertension in most subjects, and pustular rash in 17% of subjects. (Forsyth, 1993, 277; Uhl, 2006, 17) Allergic reactions, including swelling of the floor of the mouth, were noted in 3%. In addition, hydroxocobalamin therapy transiently interferes with a number of common laboratory assays. (Curry, 1994, 65)

In a clinical trial of non-poisoned human volunteers, sodium thiosulfate caused vomiting in approximately half of subjects, but did not produce life-threatening toxicity. (Forsyth, 1993, 277)

Acknowledgements:

Citation List

Baud, 1991, 1761

This prospective case series demonstrated that significant cyanide poisoning may occur as a result of smoke inhalation in house fires. Patients were generally treated with hydroxocobalamin + sodium thiosulfate. Results described as superior to loosely-defined historical controls. LOE 4.

Borron, 2007, 794

This was a prospective, open-label study in which hydroxocobalamin was administered to patients with suspected cyanide poisoning due to smoke inhalation. Most received hydroxocobalamin prior to hospital arrival. 15 patients had cardiac arrest. Because this study used only a loosely defined group of historical controls, it is difficult to determine whether the 67% rate of survival to hospital discharge in this cohort represented an improvement over that expected with supportive care and oxygen alone. Similarly, given that only 2/15 patients (13%) who received treatment following cardiac arrest survived to hospital discharge (albeit both with neurologically intact survival), it is unclear whether outcomes with hydroxocobalamin are better than those that would have been produced with standard resuscitation and supportive care alone. The control group is so ill-defined that this is better considered a prospective case series than a comparative trial. LOE 4.

Borron, 2007, 551

This was a retrospective case series of patients who developed cyanide poisoning (not in the setting of smoke inhalation), survived to ICU admission, and then received hydroxocobalamin therapy. Because this study used only an undefined group of historical controls, it is difficult to determine whether the 71% rate of survival to hospital discharge in this cohort represented an improvement over that expected with supportive care and oxygen alone. This is better considered a case series than a controlled study. LOE 4.

Chen, 1952, 113

This retrospective case series is essentially a compilation of anecdotal case reports of the use of nitrates + thiosulfate. Although most patients survived and the author asserts benefit, insufficient data are presented to determine whether the outcomes would have been the same with supportive care alone. This, combined with the substantial advances in resuscitation and critical care in the 50+ years since these cases were compiled, makes this report of little help. LOE 4.

Espinoza, 1992, 65
This report describes a single event in which 8 children, aged 8 – 11 years, developed acute cyanide poisoning from ingestion of cassava. Most children had severe cardiovascular toxicity, including hypotension, bradycardia, and respiratory failure. Because of a shortage of antidote availability, 4 children received HC and 4 received N + ST. All children improved rapidly and survived to hospital discharge, neurologically intact. LOE 4.

Fortin, 2006, 37

This was a retrospective case series of patients who received hydroxocobalamin for suspected cyanide poisoning in the setting of smoke inhalation. It is greatly limited by the fact that the ultimate outcomes of 29 (35%) of the 84 patients who were brought to the hospital alive could not be determined; therefore, the rate of survival to hospital discharge in this group may have been as low as 42% or as high as 70%. Most relevant to this review are the data that ROSC was achieved in 21 (55%) of the 38 patients found in cardiac arrest. Because this study used only a loosely defined group of historical controls, it is difficult to determine whether the outcomes in this cohort represented an improvement over that expected with supportive care and oxygen alone. LOE 4.

Houeto, 1995, 605

The primary objective of this study was to determine the dose of HC required to reduce free cyanide levels to zero. With the exception of the single patient whose blood CN concentration was 96 micromol/L, no patient in this study had severe or life-threatening poisoning. Nonetheless, this study did find that the dose of HC typically given to adults (5 grams, repeated if needed) is appropriate in the setting of accidental CN poisoning due to smoke inhalation. LOE 4.

Kirk, 1993, 1413

This small retrospective case series is valuable because it addresses an important safety concern involving the use of nitrites in smoke inhalation patients. However, it provides little information about the efficacy of N + ST therapy. LOE 4.

Pontal, 1982, 90

This retrospective case series included very dissimilar cases; it is difficult to extract data about severely poisoned patients, except that some patients with life-threatening cardiovascular toxicity improved after HC + ST administration. There was is no control group. LOE 4.

Yen, 1995, 524

This retrospective case series contains patients who received N + ST and patient who received supportive care only. It was underpowered to determine a benefit (or harm) from treatment, and also contained insufficient detail about pretreatment severity to allow for critical comparisons. LOE 4.

Studies not included in the evidence table, Consensus on Science, or Treatment Recommendations

Berlin, 1976, 793

This is a case report of iatrogenic death of a 17-month old child who ingested what was later determined to be a nontoxic amount of cyanide-containing reagent. After he received two doses of nitrite totaling 28 mg/kg (recommended dose: 15 mg/kg), the patient developed vomiting, apnea, seizures, and then cardiopulmonary arrest.

Cottrell, 1978, 809

This was a human clinical trial involving a dose of cyanide (as a metabolite of sodium nitroprusside) that was significantly less than that associated with human toxicity. As such, it does not provide information about the management of cardiac arrest or life-threatening cardiovascular toxicity due to CN poisoning, and was not included in the evidence table.

**Curry, 1994, 65**

This human trial in non-poisoned volunteers examined the interference of HC with common laboratory assays. It was neither a safety nor an efficacy study.

**Forsyth, 1993, 277**

Although this study reports alterations in whole blood cyanide levels, these subjects did not have acute cardiovascular toxicity from cyanide poisoning; the cyanide exposure came from heavy cigarette smoking. This study is best regarded as a Phase I safety study.

**Houeto, 1996, 397**

This companion to the Houeto, 1995, 605 paper, examines the pharmacokinetics of HC when administered to patients with medically significant (though usually not life-threatening) CN poisoning. Because of the overlap with the companion manuscript, we did not include this report in the evidence table.

**Pasch, 1983, 77**

This was primarily a safety and pharmacokinetic study. The CN concentrations produced by the sodium nitroprusside infusion were significantly below the levels commonly associated with severe human poisoning. Neither cardiac arrest nor life-threatening cardiovascular toxicity were studied. Because the clinical scenario employed here differs so substantially from acute severe human poisoning, this report was not included in the evidence table.

**Uhl, 2006, 17**

This well-conducted Phase I safety study was conducted in non-poisoned patients.