Carbon Monoxide, Cyanide, and Hydrogen Sulfide Antidote Treatment Clinical Questions

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What are we talking about?

- Hyperbaric oxygen for carbon monoxide?
- Antidotes for cyanide toxicity?
- Treatment of hydrogen sulfide toxicity?
Carbon monoxide toxicity

- A common problem throughout the world
  - Can have high mortality for adults and children
- Often associated with appliances in a house or business
- Cellular asphyxiant with multi-organ dysfunction
- Treatment is primarily removal from the source
- Normobaric oxygen
- What about hyperbaric oxygen?
Hyperbaric oxygen therapy

- 100% oxygen at supratherapeutic atmospheric conditions
- ~ 20 min at 3.0 ATA
- Interrupt delayed injury cascade
  - Goal is to reduce delayed neurological sequelae
- Limited resources
- Evidence equivocal
- Can be technically difficult
  - Intubated patients
Mortality (Huang 2017)

- Retrospective, observational study of a poison database with 25000 patients
- HBO₂ had significantly lower mortality than those without ( [aHR] 0.74, 95% CI 0.67 to 0.81)
  - Benefit most pronounced for patients with acute respiratory failure (aHR 0.45) and patients younger than 20 yrs old (aHR 0.43)
  - Big limitations…..
Delayed neurologic sequelae (DNS)

- Delayed Neuropsychiatric Syndrome
  - HBO$_2$ MAY be beneficial for DNS
- Earlier is probably better
- Studies are contradictory to each other
- Prospective, randomized trials come to different conclusions
- Many limitations on randomized trials
- Maybe for “sicker” people (whatever that means)

### Studies HBO₂

**TABLE 1. SUMMARY OF STUDIES COMPARING NORMOBARIC WITH HYPERBARIC 100% OXYGEN FOR TREATMENT OF CARBON MONOXIDE POISONING**

<table>
<thead>
<tr>
<th>Study (Ref. No.)</th>
<th>Year</th>
<th>Design</th>
<th>Intervention</th>
<th>Result</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raphael and colleagues (44)</td>
<td>1989</td>
<td>Randomized; if LOC, HBO₂ used</td>
<td>HBO₂ (2.0 ATA) vs. 6 h mask O₂ if no LOC; 1 HBO₂ vs. 2 HBO₂ if LOC</td>
<td>No difference in symptoms between groups at 1 mo</td>
<td>343</td>
</tr>
<tr>
<td>Ducasse and colleagues (45)</td>
<td>1995</td>
<td>Randomized, not blinded</td>
<td>HBO₂ (2.5 ATA) vs. mask O₂</td>
<td>HBO₂ improved cerebral blood flow reactivity to acetazolamide</td>
<td>26</td>
</tr>
<tr>
<td>Thom and colleagues (46)</td>
<td>1995</td>
<td>Randomized, not blinded, excluded LOC</td>
<td>HBO₂ (2.9 ATA) vs. mask O₂</td>
<td>No sequelae in HBO₂ vs. 23% for mask O₂; NNT = 4.3</td>
<td>65</td>
</tr>
<tr>
<td>Scheinkestel and colleagues (48)</td>
<td>1999</td>
<td>Double-blind RCT; cluster randomization; included LOC</td>
<td>3 to 6 HBO₂ (2.8 ATA) sessions vs. 3 d of mask O₂</td>
<td>Very high number lost to 1 mo follow-up (54%), limiting any conclusion</td>
<td>191</td>
</tr>
<tr>
<td>Mathieu and colleagues (47)</td>
<td>1996</td>
<td>Randomized, not blinded, excluded LOC</td>
<td>HBO₂ vs. mask O₂</td>
<td>Abstract only—HBO₂ reduced sequelae at 1 and 3 mo; none at 1 yr</td>
<td>575</td>
</tr>
<tr>
<td>Weaver and colleagues (49)</td>
<td>2002</td>
<td>Double-blind randomized, included LOC</td>
<td>3 HBO₂ (3 ATA for initial) in 24 h vs. 100% O₂ + 2 sham chamber sessions</td>
<td>Reduced cognitive sequelae (25 vs. 46%) at 6 wk (OR, 0.39; 95% CI, 0.2–0.78; P = 0.007); NNT = 4.8; with significant differences persisting to 12 mo</td>
<td>152</td>
</tr>
<tr>
<td>Ananne and colleagues (50)</td>
<td>2011</td>
<td>Randomized, not blinded</td>
<td>Trial 1: HBO₂ session (2.0 ATA) + 4 h mask O₂ vs. 6 h mask O₂ if transient LOC Trial 2: 2 HBO₂ + 4 h mask O₂ vs. 1 HBO₂ + 4 h mask O₂ if initial coma</td>
<td>Outcomes measured by symptom questionnaire and physical examination at 1 mo. Trial 1—no difference in outcome as measured. Trial 2—“complete recovery” rate 47% with 2 HBO₂ vs. 68% with 1 HBO₂</td>
<td>385</td>
</tr>
</tbody>
</table>

*Definitions of abbreviations: ATA = atmosphere absolute; CI = confidence interval; HBO₂ = hyperbaric oxygen; LOC = loss of consciousness; NNT = number needed to treat; OR = odds ratio; RCT = randomized controlled trial.*
Does HBO$_2$ prevent DNS?

**Yes**
- Many textbooks
- Many “experts”
- Most Undersea Medicine Groups
- Many US editorials (almost)
- All lawyers

**Equivocal**
- American College of Emergency Medicine Clinical Policy
- Cochrane collaboration (x2)
- International Liaison Committee on Resuscitation (ILCOR)
- Australian government
- German government

UNDERSEA & HYPERBARIC MEDICAL SOCIETY
Raising the quality of practice one member at a time
Consider HBO$_2$ (not prospectively studied)

- Consider HBO$_2$ (if available)
  - Loss of consciousness
  - Altered mental status (in the ED)
  - End organ ischemia (EKG changes, pH<7.1, etc)
  - COHgb >25%
- Lower threshold for pregnant patients
  - 20% COHgb

2. In ED patients diagnosed with acute CO poisoning, does HBO$_2$ therapy as compared with normobaric oxygen therapy improve long-term neurocognitive outcomes?

Patient Management Recommendations

*Level A recommendations.* None specified.

*Level B recommendations.* Emergency physicians should use HBO$_2$ therapy or high-flow normobaric therapy for acute CO-poisoned patients. It remains unclear whether HBO$_2$ therapy is superior to normobaric oxygen therapy for improving long-term neurocognitive outcomes.

*Level C recommendations.* None specified.

ACEP 2017
Pregnant patients

A MULTICENTER, PROSPECTIVE STUDY OF FETAL OUTCOME FOLLOWING ACCIDENTAL CARBON MONOXIDE POISONING IN PREGNANCY

GIDEON KOREN,* TERESA SHARAV, ANNE PASTUSZAK,* LORNE K. GARRETTSON,† KELLY HILL, IVAN SAMSON, MARK ROREM, ARLENE KING and JILL E. DOLGIN‡

- Increased concern for pregnant women and fetus
- Mild to moderate toxicity no adverse outcomes to babies
- 5 with severe toxicity, 3 with normobaranic poor outcome, 2 with HBO₂ did better
- Very minimal literature

Koren 1991
Cyanide toxicity

- Hydrogen cyanide gas, solid cyanide salts
- "Take down agent"
- Inhalation of gas >> ingestion >> dermal
- Cellular hypoxia by inhibition of mitochondrial cytochrome c oxidase with metabolic acidosis and elevated lactate
- Central nervous system
  - Headache, confusion, agitation, syncope, seizures, coma, death
- Cardiovascular
  - Tachycardia, hypertension, bradycardia, hypotension, cardiac arrest
- Treatment
Cyanide antidote kit

- Amyl nitrite
  - Create methemoglobin to bind CN
  - Concern of creating MetHgb if CO presents
  - Hypotension
- Sodium nitrite
- Sodium thiosulfate
  - Metabolic cofactor
  - Detoxification of cyanide to thiocyanate
  - Minimal adverse events

Chen 1932, 1952, Gracia 2004
Nitrite-thiosulfate

- Dog study showing nitrite and thiosulfate increased LD$_{50}$ 18-fold
- Early reports of cases of human CN toxicity rescued by nitrites/thiosulfate

- Multiple cases and suggested treatment for CN toxicity
Nitrite and sodium thiosulfate

Lam and Lau (2000) Poisoning by inhalation of hydrogen cyanide in a chemical trading company office where flasks containing diluted hydrocyanic acid had been left uncovered. A 19-year-old woman was found unconscious, hypotensive, and tachycardic with severe metabolic acidosis. An amyl nitrite pearl was administered followed by sodium thiosulfate 12.5 g. In the intensive-care unit, the patient had repeated seizures requiring anticonvulsant therapy. She was extubated 15 hours after admission.

Survival with no sequelae

Lam and Lau (2000) Poisoning by inhalation of hydrogen cyanide in a chemical trading company office where flasks containing diluted hydrocyanic acid had been left uncovered. A patient who tried to rescue the 19-year-old victim described above was exposed to the cyanide fumes for approximately 10 minutes. He was sent to the emergency department with severe dizziness and near syncope. The patient was given an amyl nitrite pearl followed by sodium nitrite and sodium thiosulfate. The patient recovered and was discharged 3 days later.

Survival with sequelae of mild impairment of recent memory and concentration at 1-year follow-up

Chin and Calderon (2000) Attempted homicide by cyanide ingestion (concentration not reported). A 19-year-old woman presented to the emergency department unresponsive, in shock, and with severe metabolic acidosis. Initial treatment with 12.5 g sodium thiosulfate was associated with improvement of acidosis. The patient was next treated with sodium nitrite and more sodium thiosulfate and supportive measures.

Survival with sequelae of hair loss, short-term memory problems, and bradycardia

Ruangkanchanasetr et al. (1999) Cyanide poisoning from ingestion of boiled cassava. A 4-year-old girl vomited and became comatose 9 hours after ingestion of boiled cassava. The patient was intubated and given ventilatory support at a community hospital and then was transferred to an intensive care unit. Nineteen hours after ingestion, sodium thiosulfate and sodium nitrite were given. The patient recovered normal breathing the next day. Blood cyanide concentration at arrival at the intensive care unit was 0.56 µg/mL.

Survival with no sequelae

Wurzburg (1996) A case series of three El DuPont company employees exposed to cyanide and given sodium nitrite and sodium thiosulfate, usually within 3 minutes of exposure.

Survival with side effects of headache and loss of appetite

Goodhart (1994) Poisoning by ingestion of potassium-gold cyanide solution containing approximately 1650 mg of potassium cyanide. The 54-year-old patient was administered amyl nitrite, sodium nitrite, and sodium thiosulfate with hyperbaric oxygen.

Survival with no sequelae

Scolnick et al. (1993) A case series of two individuals poisoned by exposure to propionitrile fumes at an organic chemical manufacturing plant. One victim was comatose, acidic, and hypotensive. He regained consciousness after infusion of sodium nitrite/sodium thiosulfate. Another victim never lost consciousness but had nausea, dizziness, and headache. Blood cyanide concentrations were 5.0 and 3.5 µg/mL, respectively.

Survival with no sequelae

Nakatani et al. (1993) Poisoning by ingestion of potassium cyanide. A 31-year-old male was found comatose and having seizures. Three pearls of amyl nitrite were administered followed by sodium thiosulfate 10 g over 15 minutes. The patient revived 1.5 hours after treatment.

Survival with no sequelae

Turchen et al. (1991) Poisoning by ingestion of acetonitrile-containing cosmetic. A 38-year-old woman ingested Super Nail Nail Off 59 mL (containing 99% acetonitrile) in an attempted suicide. After approximately 12 hours, the patient developed seizures and had severe metabolic acidosis. Sodium thiosulfate and sodium nitrite were given. Administration of sodium nitrite was associated with bradycardia and hypotension. Several relapses over the course of hospitalization were treated successfully with sodium thiosulfate. The patient was fully recovered by the fifth day in the hospital.

Survival with no sequelae

Johnson et al. (1989) Poisoning by ingestion of potassium cyanide (unknown amount). A 24-year-old woman attempted suicide by ingesting potassium cyanide. Administration of amyl nitrite+sodium nitrite+sodium thiosulfate was associated with full recovery. Blood cyanide concentration approximately 1 hour after ingestion was 13 µg/mL.

Survival with no sequelae

Hall et al. (1987) Poisoning by ingestion of potassium cyanide 1 g. A 34-year-old man attempted suicide by ingesting potassium cyanide. Within 1 hour after ingestion, the patient was in a coma and apneic with metabolic acidosis and seizures. Sodium thiosulfate and sodium nitrite were administered. Clinical improvement was observed by the end of the infusion.

Survival with no sequelae

Chen and Rose (1956) Poisoning by exposure to hydrocyanic acid after house fumigation. A 41-year-old woman collapsed and vomited while rescuing a child from a house being fumigated with hydrocyanic acid. Four hours after initial treatment with amyl nitrite inhalation and sodium thiosulfate 600 mg, the patient was stuporous with a slow respiratory rate. Additional treatment administered over 3 days included methylene blue, sodium nitrite, and sodium thiosulfate. The patient was released from the hospital 8 days after the poisoning.

Survival with sequelae of persistent headache and backache
IM use

Sodium Nitrite and Sodium Thiosulfate Are Effective Against Acute Cyanide Poisoning When Administered by Intramuscular Injection

Vikhyat S. Bebarta, MD; Matthew Brittain, PhD; Adriano Chan, BS; Norma Garrett, PhD; David Yoon, MS; Tanya Burney, BS; David Mukai, BS; Michael Babin, DVM; Renate B. Pilz, MD; Sari B. Mahon, PhD; Matthew Brenner, MD; Gerry R. Boss, MD*

• Potential use out-of-hospital or in mass casualty situation
  • Animal study, 3 groups (mice, rabbits, pigs) received saline or IM sodium nitrite/sodium thiosulfate
  • Sodium nitrite and sodium thiosulfate rescued 100% of the mice, 73% of the rabbits and 80% of the pigs.
  • Unsure implications for humans

Bebarta 2016
Hydroxocobalamin

• Natural form of vitamin $B_{12}$
• Contains cobalt moiety that binds to intracellular cyanide
• Forms cyanocobalamin
• Does not adversely affect tissue oxygenation
  - Minimal adverse events
• 70 mg/kg (typical adult dose is 5 g)
• Addition of thiosulfate

Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation

Stephen W. Borron MD, MSa, Frédéric J. Baud MDb,c,*, Bruno Mégarbane MD, PhDb, Chantal Bismuth MDc

• Retrospective review of patients admitted to ICU after presumed cyanide toxicity
  • 10/14 (71%) survived and were discharged
  • Of 11 patients with blood cyanide exceeding the typically lethal threshold of 100 lmol/L, 7/11 64% survived.
  • Most common adverse events were chromaturia and pink skin discoloration.

Borron 2007
• Prospective study of smoke-inhalation patients who received hydroxocobalamin
  • 50/69 patients (72%) survived after administration of hydroxocobalamin.
• Confirmed CN poisoning (28/42) 67% survived after administration of hydroxocobalamin
  • Most common adverse events were chromaturia, pink or red skin, and hypertension
  • No serious adverse events attributed to hydroxocobalamin

Borron 2007
Hydrogen sulfide (H₂S)

- Naturally produced by the putrefaction of organic matter as well as industrial sources
- “Detergent suicide”
- Rotten-egg smell wanes as olfactory fatigue occurs in seconds
- Cellular hypoxia by inhibition of mitochondrial cytochrome c oxidase with metabolic acidosis and elevated lactate
- Conjunctivitis, pulmonary edema, CNS toxicity (knockdown), cardiovascular collapse
- Treatment is removal from the source and supportive

Antidotes?
Hydroxocobalamin for $\text{H}_2\text{S}$

High-dose hydroxocobalamin administered after $\text{H}_2\text{S}$ exposure counteracts sulfide-poisoning-induced cardiac depression in sheep

PHILIPPE HAOUZI,\textsuperscript{1} BRUNO CHENUEL,\textsuperscript{2} and TAKASHI SONOBE\textsuperscript{1}

• 2 groups of sheep, given known lethal dose of $\text{H}_2\text{S}$
• 8 received saline and 8 received hydroxocobalamin after cessation of infusion
• 3 animals died (1 control, 2 hydroxocobalamin) died prior to being given drug/saline
  • 71% (5/7) died in the control group by cardiac arrest within 10 min
• 6/6 of animals who got hydroxycobalamin (all within 1-4 min after cessation of $\text{H}_2\text{S}$) survived, however, no evidence of recovery in oxidative metabolism in the group receiving hydroxocobalamin was seen

Haouzi 2015
20 yr old male, suicide by creating $\text{H}_2\text{S}$ in his car, cardiac arrest on arrival hospital

He was given hydroxocobalamin (and CPR) but died approximately 42 min after arrival.

Serum concentrations of sulfide dropped from 0.22 to 0.11 $\mu$g/mL after antidote.

Serum concentrations of thiosulfate dropped from 0.34 and 0.04 $\mu$mol/mL, after antidote.
Methemoglobin induction

- Formation of MetHgb by nitrites creates a large pool of ferric iron
- Ferric has a higher affinity for sulfide than cytochrome c
- Cytochrome c able to reactivate
- However, H$_2$S rapidly moves from blood to tissue which likely limits utility of MetHgb treatment
MetHgb induction

Effects of infusion of human methemoglobin solution following hydrogen sulfide poisoning

B. CHENUEL, T. SONOBE, and P. HAOUZI

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Pennsylvania State University College of Medicine, Hershey, PA, USA

• Prior study showed decreased H₂S after inducing methemoglobin
  • However, this was during infusion of H₂S
• Induction of MetHgb 90sec after cessation of H₂S did not change H₂S blood concentrations
• No improvement in H₂S-induced lactic acidosis or return of carotid blood flow
Alternative or new treatment
Isocapnic hyperpnea for CO

- Hyperventilation with a normobaric mixture of oxygen and a small amount of CO2
- Maintain a PaCO$_2$ of approximately 40 mmHg despite a sixfold increase in minute ventilation
- Animal model showed double the elimination of CO versus 100% FiO$_2$
- Non-intubated volunteer study showed similar elimination
- Very unproven but technically easy

Figure 2. Percent COHb versus time for a representative subject (Δ in Figure 3) during exposure to CO and treatment with 100% O$_2$, normal ventilation (N-O$_2$, open triangles), and normocapnic hyperpnea (NH-O$_2$, closed triangles).

Fisher 1999, Takeuchi 2000
Cobinamide for cyanide and \( \text{H}_2\text{S} \)

- Vitamin \( B_{12} \) analog
- Binds CN similar to hydroxocobalamin
- Has 2 binding sites
- More water soluble so less volume needed
- May be able to be used orally (Lee 2015)
- Another option for treatment of toxins with amenable mechanisms
Cobinamide

Intravenous Cobinamide Versus Hydroxocobalamin for Acute Treatment of Severe Cyanide Poisoning in a Swine (Sus scrofa) Model

Lt Col Vikhyat S. Bebarta, MC, USAF*; David A. Tanen, MD; Susan Boudreau, RN, BSN; Maria Castaneda, MS; Lee A. Zarzabal, MS; Toni Vargas, PA-C; Gerry R. Boss, MD

*Corresponding Author. E-mail: vikbebarta@yahoo.com.

• Control (saline), hydroxocobalamin, and cobinamide given to CN-poisoned swine
• 2/11 control animals survived compared with 10/11 in each of the hydroxocobalamin and cobinamide groups
• Time to return of spontaneous breathing was similar between hydroxocobalamin and cobinamide
  • Blood cyanide concentrations became undetectable at the end of the study
    • Much lower dose of cobinamide

Bebarta 2014
Cobinamide

Efficacy of Intravenous Cobinamide Versus Hydroxocobalamin or Saline for Treatment of Severe Hydrogen Sulfide Toxicity in a Swine (*Sus scrofa*) Model

Vikhyat S. Bebarta, MD, Normalynn Garrett, PhD, CRNA, FAAN, Matthew Brenner, MD, Sari B Mahon, PhD, Joseph K. Maddry, MD, Maj, MC US Air Force, Susan Boudreau, RN, Maria Castaneda, MS, and Gerry R. Boss, MD

- Control (saline), hydroxocobalamin, and cobinamide given to H$_2$S-poisoned swine
  - 8/8 cobinamide-treated patients survived while 0/8 (0%) and 0/8 (0%) of hydroxocobalamin and saline treated animals survived
- Mean (SD) time to spontaneous ventilation in the cobinamide-treated animals was 3.2 (1.1) minutes
Summary

- 100% normobaric oxygen should be started on all CO-toxic patients
- Efficacy for HBO₂ is somewhat equivocal
  - In a potentially high-risk patient, if able to be initiated early, it may be reasonable
- CN can take many forms and can have a very rapid onset
- Nitrites/thiosulfate and hydroxocobalamin/thiosulfate have animal and human case report/case series data supporting use
  - Hydroxocobalamin may be preferred with less adverse events, better tolerated, and rapid onset of action
- H₂S can often be confused with methane gas which is a simple asphyxiant
- Although the mechanism is similar CN, rapid distribution of H₂S into tissues makes it much less amenable to antidote use
- We need to continue to look at alternative treatment for these toxins
thank you

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