

Hydroxocobalamin for Suspected Cyanide Poisoning

A man is treated empirically in the ED for suspected cyanide poisoning after a fire. He is given hydroxocobalamin (HCO), an FDA-approved therapy for cyanide toxicity. Although this patient does not survive, HCO is a respected choice for empiric and definitive treatment of cyanide poisoning.

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Case

A 50-year-old man who is in cardiac arrest after being pulled out of a building fire has return of circulation en route to the ED; however, he never regains consciousness. During his prehospital resuscitation he receives intravenously a total of 3 mg of epinephrine, 40 units of vasopressin, and 1 mg of atropine. His vital signs upon arrival include a blood pressure of 110/80 mm Hg; heart rate, 105 beats/min; temperature, 36.7°C; and respiratory rate, 12 breaths/min with the patient intubated on mechanical ventilation. His oxygen saturation level is 100% on 100% oxygen. Initial laboratory analysis is remarkable for the following measurements: carboxyhemoglobin, 46%; blood lactate, 11.5 mmol/L. Arterial blood gas levels include a pH of 6.9; P_{CO_2} , 65 mm Hg; P_{O_2} , 317 mm Hg; and oxygen saturation, 88%. His physical exam does not reveal significant cutaneous burns, but there is a large amount of carbonaceous material around his mouth and nares. He is treated empirically for cyanide poisoning with 5 g of hydroxocobalamin (HCO), with no clinical improvement. About 30 minutes posttreatment, his blood pressure is 220/180 mm Hg. Approximately 2 hours after treatment, his blood pressure remains elevated, at 185/79 mm Hg, and he receives nicardipine by IV infusion. He subsequently receives hyperbaric oxygen therapy, but on hospital day 7 his care is withdrawn following documentation

of brain death. Blood is sent for analysis of the cyanide concentration.

What is HCO, and what is its use?

The ability of cobalt ion to chelate cyanide has been known for many years.¹ HCO is a cobalt-containing compound that is a precursor to cyanocobalamin (which is vitamin B₁₂). It contains an OH group in place of a CN group at the cobalt-binding site of the molecule. HCO binds cyanide, displacing the OH, to form the vitamin, which is then rapidly eliminated in the urine. HCO was approved by the FDA in 2006 for the treatment of cyanide poisoning. It is currently marketed as Cyanokit and is packaged as a lyophilized powder that requires reconstitution with normal saline. In many regions it has replaced the classic three-part cyanide antidote kit (CAK) for the treatment of presumed cyanide poisoning.

What are the expected clinical features of cyanide toxicity?

Cyanide exposure can occur through several different routes: inhalation, ingestion, dermal, or parenteral. Cyanide inhibits multiple enzymes—most importantly, mitochondrial cytochrome oxidase (a-a₃ position), causing an arrest of oxidative phosphorylation. This disrupts the ability of electrons to bind to their final acceptor, oxygen, at the terminal end of the electron transport chain. Despite adequate oxygenation of the blood, oxygen cannot be utilized by the tissue, and ATP (adenosine triphosphate) cannot be produced. As a consequence, cellular hypoxia occurs. A shift toward anaerobic metabolism leads to metabolic acidosis with an increased lactic acid concentration (>10 mmol/L).²

Acute cyanide poisoning manifests with rapid-onset neurologic findings such as headache, anxiety, agitation,

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confusion, lethargy, seizures, coma, and early tachypnea followed by bradypnea. The cardiovascular effects of cyanide poisoning may initially cause hypertension and bradycardia, followed by hypotension with a reflex tachycardia, although hypotension and bradycardia are the preterminal events. The rate of onset is related to the route of exposure; inhalation of gaseous hydrogen cyanide results in nearly immediate collapse, while ingestion of a cyanide salt, such as sodium cyanide, may not cause clinical effects for up to 20 minutes.

Why was this patient treated empirically for cyanide poisoning with HCO?

Fire victims may be exposed to hydrogen cyanide, which is liberated from the burning of materials such as wool, plastics, nylon, and polyurethane found in automobiles, carpets, home furniture, and appliances. Cyanide poisoning can be difficult to diagnose clinically in fire victims due the multifactorial nature of smoke exposure and the presence of concomitant traumatic injury and medical conditions (eg, intoxication). In fire victims without significant burns, a lactate level greater than 10 mmol/L upon arrival in the ED is a sensitive marker for an elevated blood cyanide concentration (and, by analogy, cyanide poisoning). But fire victims often concurrently suffer from carbon monoxide poisoning, asphyxia, trauma, and thermal injury, all of which produce findings that may be indistinguishable from cyanide poisoning.

The patient received HCO in the ED, due to his dramatic clinical and laboratory findings (eg, arrival lactic acid level >10 mmol/L). In this case, HCO is a superior choice compared with the traditional

CAK, due to the presence of significant carbon monoxide hemoglobin concentrations. The CAK consists of amyl nitrite, sodium nitrite, and sodium thiosulfate. The nitrites oxidize a small percentage of normal hemoglobin to methemoglobin (Hb³⁺), which has a higher affinity for cyanide

than for the mitochondrial cytochromes. Sodium thiosulfate provides a sulfur moiety for rhodanese, the enzyme that fosters the reaction of sulfur compounds with cyanide to form thiocyanate, a relatively nontoxic metabolite that is eliminated renally. In fire

victims who may have elevated carboxyhemoglobin concentrations, the induction of methemoglobinemia is potentially devastating, as both aberrant forms of hemoglobin inadequately deliver oxygen to the tissues. Administration of the thiosulfate portion of the CAK may prove beneficial and is often recommended, although it has not been formally evaluated in clinical trials. Animal data suggest a synergistic effect of sodium thiosulfate and HCO, but the two therapies have never been studied head-to-head.

Why did this patient develop hypertension?

There are several plausible explanations. Several of the medications administered during the prehospital arrest cause hypertension. However, vasopressin and epinephrine have plasma half-lives of 10 to 20 minutes and 2 to 5 minutes, respectively, and it is unlikely that their effect would last 2 hours. Atropine should not have a profound effect on blood pressure.

Hypertension is a recognized effect of HCO; it results from the ability of HCO to bind nitric oxide (NO) to form nitrocobalamin. Nitric oxide normally relaxes vascular smooth muscle tone, causing vasodilation. By scavenging NO, HCO causes vasoconstriction and hypertension.³

In healthy, non-cyanide-poisoned individuals, HCO causes a significant elevation in blood pressure. In one randomized study, IV doses of 2.5, 5, 7.5, and 10 g of HCO were administered to 102 subjects alongside a control group of 34 placebo recipients (Table).⁴ The clinical implications of a transient rise in blood pressure are not known but unlikely to be consequential in most patients.

In addition to the significant mean increases seen in the Table, maximum changes in systolic and diastolic blood pressure of 57 and 52 mm Hg, respectively, were observed. Little information on the duration of these changes was reported. The authors indicated that blood pressure “typically” returned to baseline by 4 hours postinfusion, but in one patient, persistent elevation to 166/112 mm Hg was noted at 72 hours. The authors concluded that the changes in blood pressure were clinically insignificant, but it is not yet clear how to apply the data gathered from this small number of patients to the general (ie, less healthy) population.

An elevation in blood pressure is likely desirable in hypotensive fire (or cyanide-poisoning) victims, suggesting the importance of proper selection of pa-

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TABLE. Maximum Mean Blood Pressure Changes After HCO Administration in Healthy Volunteers

HCO Dose	Total Patients	Systolic BP (SD)	Diastolic BP (SD)
2.5 g	9	22.9 (18.7) mm Hg	14.3 (8.3) mm Hg
5 g	66	22.6 (16.8) mm Hg	17.7 (9.8) mm Hg
7.5 g	9	27.0 (10.0) mm Hg	25.4 (4.7) mm Hg
10 g	18	25.7 (13.2) mm Hg	22.6 (10.1) mm Hg

HCO = hydroxocobalamin; BP = blood pressure; SD = standard deviation.
Adapted from Uhl et al.⁴

tients to receive this drug. However, the difficulty in diagnosing cyanide poisoning in a clinically useful time frame suggests that most patients must be treated empirically. The clinical diagnosis of consequential cyanide poisoning could reasonably be assumed in a fire victim with altered mental status and hypotension, particularly if significant carbon monoxide poisoning and trauma can be rapidly excluded.

In this case, the aforementioned serum sample obtained prior to HCO administration revealed no detectable concentration of cyanide.

Can HCO therapy result in other adverse effects?

Other commonly recognized adverse effects include chromaturia, skin redness, pustular/papular rash, headache, injection site reaction, lymphocyte count decrease, nausea, chest discomfort, dysphagia, and relative bradycardia. Almost all patients who receive this therapy display a predictable red discoloration of their skin and urine, which is not surprising given the deep red color of HCO itself. Impressive color images illustrating this effect may be found in the literature.⁵ Although the color-associated effects of HCO administration might seem simply cosmetic to the patient, they may render several colorimetric laboratory tests useless. The most clinically significant interference occurs with carbon monoxide oximetry (co-oximetry), in which carboxyhemoglobin measurement, which provides critical information in fire victims, will be inaccurate.⁶

In addition, levels of creatinine, bilirubin, triglycerides, cholesterol, total protein, and glucose may be falsely increased, and unpredictable alterations may occur in other laboratory values, such as phosphate, aspartate aminotransferase, and creatine kinase concentrations. It is essential to obtain blood for analytical testing before the administration of HCO. Saving a victim's life, however, should generally take priority.

What protocols currently exist for the use of HCO?

HCO has gained general acceptance as treatment for presumed cyanide poisoning in fire victims in the prehospital setting. The New York City Fire Department EMS has adopted a protocol for this use of HCO. The protocol calls for initiation of treatment for suspected cyanide toxicity in patients who demonstrate any of the following after exposure to smoke in an enclosed space: hypotension not attributable to other obvious causes, altered mental status, coma, seizures, respiratory arrest, or cardiac arrest. As part of the protocol, before administration of HCO, blood samples are collected in the following three tubes: a fluoride oxalate whole-blood tube (gray), a K₂-EDTA tube (purple), and a lithium heparin tube (green). The gray tube is used primarily for the determination of blood cyanide concentration, which cannot be determined after HCO treatment.

Conclusion

HCO is quickly becoming the therapy of choice

for empiric and definitive treatment of patients with cyanide poisoning. Given its relatively short history of use and potential adverse effects, cautious administration remains essential, and all cases involving adverse effects should be reported to the regional poison control center. Further study of both its beneficial and adverse effects should remain a priority. □

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