

Hydroxocobalamin for Cyanide Poisoning

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Case Summary:

A 50 year-old man, in cardiac arrest after being pulled out of a building fire, has return of circulation en route to the ED, though he never regains consciousness. During his pre-hospital resuscitation he receives intravenously a total of 3 mg of epinephrine, 40 units of vasopressin and 1 mg of atropine prior to arrival in the ED. His initial vital signs upon arrival are BP, 110/80 mmHg; HR, 105 beats/min; Temp, 98.0° F; RR, 12/min, intubated on mechanical ventilation; O₂ saturation, 100% on 100% O₂. Initial laboratory analysis is remarkable for: carboxyhemoglobin, 46%; blood lactate, 11.5 mmol/L; and ABG: pH, 6.9; pCO₂, 65; pO₂, 317, O₂ 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 5g of hydroxocobalamin (HCO), with no clinical improvement. About 30 min after its administration, his blood pressure is noted to be 220/180 mmHg. Approximately two hours later his blood pressure remains elevated at 185/79 mmHg, for which he receives nicardipine by intravenous 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 He subsequently receives hyperbaric oxygen therapy, but on hospital day 7 his care is withdrawn following documentation of brain death.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 more than one hundred years. HCO, a cobalt containing compound that is a precursor to cyanocobalamin (which is vitamin B₁₂), that 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 this vitamin, which is then rapidly eliminated in the urine. Hydroxocobalamin was approved in 2006 by the FDA in the US for the treatment of cyanide poisoning. It is currently marketed as Cyanokit®, and is packaged as a lyophilized powder which requires reconstitution with normal saline.

What are the expected clinical features of cyanide toxicity?

Patients may be exposed to cyanide by several different routes: inhalation, ingestion, dermal, and parental. Cyanide inhibits multiple enzymes most importantly mitochondrial cytochrome oxidase (a-a₃ position), causing an arrest of oxidative phosphorylation. This disrupts the ability 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 cannot be produced. As a consequence, cellular hypoxia occurs. A shift toward anaerobic metabolism leads to a metabolic acidosis with an increase lactic acid concentration (>10 mmol/L).¹

Acute cyanide poisoning manifests with rapid onset neurological findings such as headache, anxiety, agitation, confusion, lethargy, seizures, coma, and early tachypnea followed by bradypnea. Cardiovascular effects of cyanide poisoning may initially produce hypertension and bradycardia, followed by hypotension with a reflex tachycardia, although hypotension and bradycardia are the pre-terminal event. The rate of onset is related to the route of exposure, with inhalation of gaseous hydrogen cyanide resulting in nearly immediate collapse, while ingestion of a cyanide salt such as sodium cyanide may not result in clinical effects for 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 to the multifactorial nature of smoke exposure and the presence of concomitant traumatic injury and medical conditions (e.g., intoxication). A lactate greater than 10 mmol/L upon arrival in the ED in fire victims without significant burns is a sensitive marker for elevated blood cyanide concentration (and by analogy, cyanide poisoning). But these patients 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 (e.g., arrival lactic acid >10 mmol/L). Hydroxocobalamin is a superior choice compared with the traditional cyanide antidote kit (CAK) in this case due to the presence of a significant COHb concentration. The CAK consists of amyl nitrite, sodium nitrite, and sodium thiosulfate. The nitrites oxidize a small percent of normal hemoglobin to methemoglobin (Hb³⁺), which has a higher affinity for cyanide than 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 non-toxic and renally eliminated metabolite. In fire victims who may have elevated carboxyhemoglobin, 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 this has not been formally evaluated in clinical trials. Animal data suggest a synergistic effect of sodium thiosulfate and HCO, but the two individual therapies have never been studied head to head.

Why did this patient develop severe and persistent hypertension?

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

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

In healthy volunteers HCO causes a significant elevation in blood pressure. In one such study, intravenous doses of 2.5, 5, 7.5, and 10 g of HCO were randomly administered to 102 subjects alongside a placebo control group of 34 subjects.² (Table 1).

Table 1: Mean changes in systolic and diastolic blood pressure in healthy volunteers after 5 g, 7.5 g, and 10 g of HCO.²

HCO dose	# of patients	Systolic BP (SD)	Diastolic BP (SD)
5 g	66	22.6 (16.8)	17.7 (9.8)
7.5 g	9	27.0 (10.0)	25.4 (4.7)
10 g	18	25.7 (13.2)	22.6 (10.1)

In addition to the significant mean increases seen in Table 1, a maximum change in systolic blood pressure of 57 mmHg, and diastolic blood pressure of 52 mmHg was observed. Very little information on the actual duration of these changes was reported. The authors indicated that the blood pressure “typically” returned to baseline by 4 hours post infusion, but persistent BP elevation in one patient to 166/112 mmHg was noted at 72 hours. Despite these findings the authors concluded that the changes in blood pressure were clinically insignificant. Without further study it is not clear how to apply this data gathered from this small number of patients to the general (e.g., less healthy) population and it may be dangerous to assume that these changes are benign. While an elevation in blood pressure in hypotensive fire victims with cyanide poisoning is desired, the value of HCO in producing this effect or its effect on outcome is not known.

The difficulty in diagnosing cyanide poisoning in a clinically useful timeframe suggests that most patients will be treated empirically. The volunteer studies suggest the potential for severe adverse event in fire victims who are not cyanide poisoned.

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

Are there other adverse effects from HCO therapy?

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 this predictable red discoloration of their skin and urine color, 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 The “color” effects of HCO administration are more than just cosmetic, as several colorimetric laboratory tests may be rendered useless. The most clinically significant interference occurs with cooximetry,

in which carboxyhemoglobin measurement, critical information in fire victims, will be inaccurate.⁴ Creatinine, bilirubin, triglycerides, cholesterol, total protein, and glucose may be falsely increased, and others such as phosphate, AST, and CK are unpredictably altered. The need to obtain blood for analytical testing before the administration of HCO is essential.

What protocols currently exist for the use of HCO in NYC?

Hydroxocobalamin has gained general acceptance as treatment for presumed cyanide poisoning in fire victims in the pre-hospital setting. FDNY-EMS recently (July 2009) adopted a protocol for this use of HCO. Indications to initiate treatment for suspected cyanide toxicity include patients who after exposure to smoke in an enclosed space demonstrate any of the following symptoms: hypotension not attributable to other obvious causes, altered mental status, coma, seizures, respiratory arrest, or cardiac arrest. As part of the FDNY-EMS protocol, the following three tubes will be drawn before administration of HCO, a fluoride oxalate whole blood tube (grey), a K₂- EDTA tube (purple), and a lithium heparin tube (green). The grey tube will primarily be used for the determination of blood cyanide concentration, which cannot be determined after HCO treatment.

In summary, HCO is quickly becoming the therapy of choice for empiric and definitive treatment of patients with cyanide poisoning. Its relatively short history of use and the potential adverse effects make it essential to be cautious with its administration, and to report all such cases to the NYCPC (or other regional PCC). Further study of adverse effects and outcome benefit should remain a priority.

Selected references:

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