



Follow-up from the New York City Poison Control Center Consultants' Conference of July 2, 2009

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 prehospital resuscitation he receives intravenously at 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 He subsequently receives hyperbaric oxygen therapy, but on hospital day 7 his care is withdrawn following documentation of brain death.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 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 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

Program Announcements ••

Ruth A. Lawrence: Monthly conference: every 4 weeks on Thursdays (11am to noon), and every 4 weeks on Tuesdays (10am-11am).

UNY: The 2009 Toxicology Teaching Day is Scheduled for 11/4/09. Please mark your calendars!!

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

Long Island Regional Poison and Drug Information Center: Please look for our summer programs

Please call administrative telephone numbers for more information.

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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 concentrations. 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 suggests 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 both 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).

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.

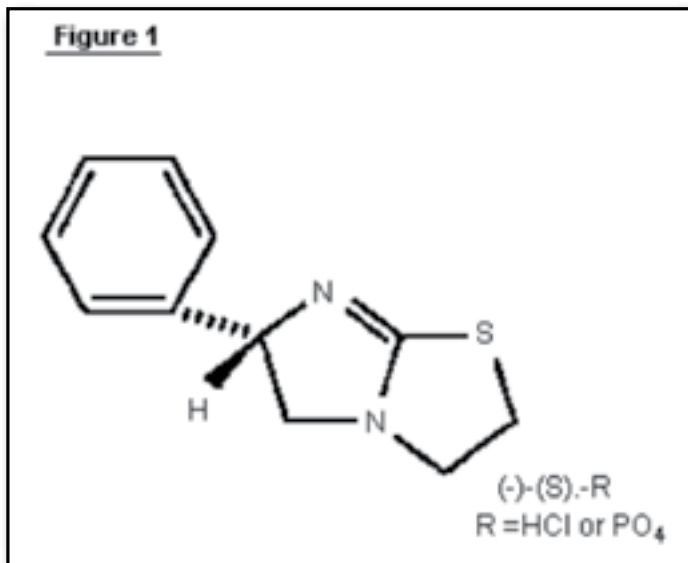
The difficulty in diagnosing cyanide poisoning in a clinically useful timeframe suggests that most patients will be treated empirically. The volunteer studies suggest the potential for severe adverse events in fire victims who are not cyanide poisoned.

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

Levamisole as an Adulterant of Cocaine: Its Possible Purpose and Adverse Reactions

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Levamisole is the levo-isomer of a broad spectrum, highly active anthelmintic agent tetramisole which was introduced in 1966^{1,2}. It was widely used in veterinary medicine for the treatment of various pulmonary and gastrointestinal pathogenic nematodes¹⁻³.



(Ref. 2)

In 1971 Renoux and colleagues discovered that levamisole possesses immunomodulatory properties in mice via potentiation of T-cell mediated immunity⁴. Further research demonstrated that this compound stimulates T-cell activity and enhances the function of B-lymphocytes and macrophages⁴.

Levamisole has since been extensively studied and utilized for a variety of immunological conditions such as SLE, rheumatoid arthritis, ulcerative colitis, Crohn's disease, and some cancers with minimal success^{3,5}. However, it is found to be useful as an adjunct in combination with fluorouracil for the treatment of advanced colon cancer after surgical resection, and was approved for this indication in the United States in 1990². In 2000, the manufacturer of levamisole voluntarily withdrew the drug from the U.S. market due to unfavorable side effect profile. Levamisole is still available outside of the U.S. for veterinary applications⁵.

Recently levamisole has reappeared in North America as an unusual adulterant of cocaine. Illicit drugs such as cocaine are often diluted with various non-pharmacologically and pharmacologically active substances:

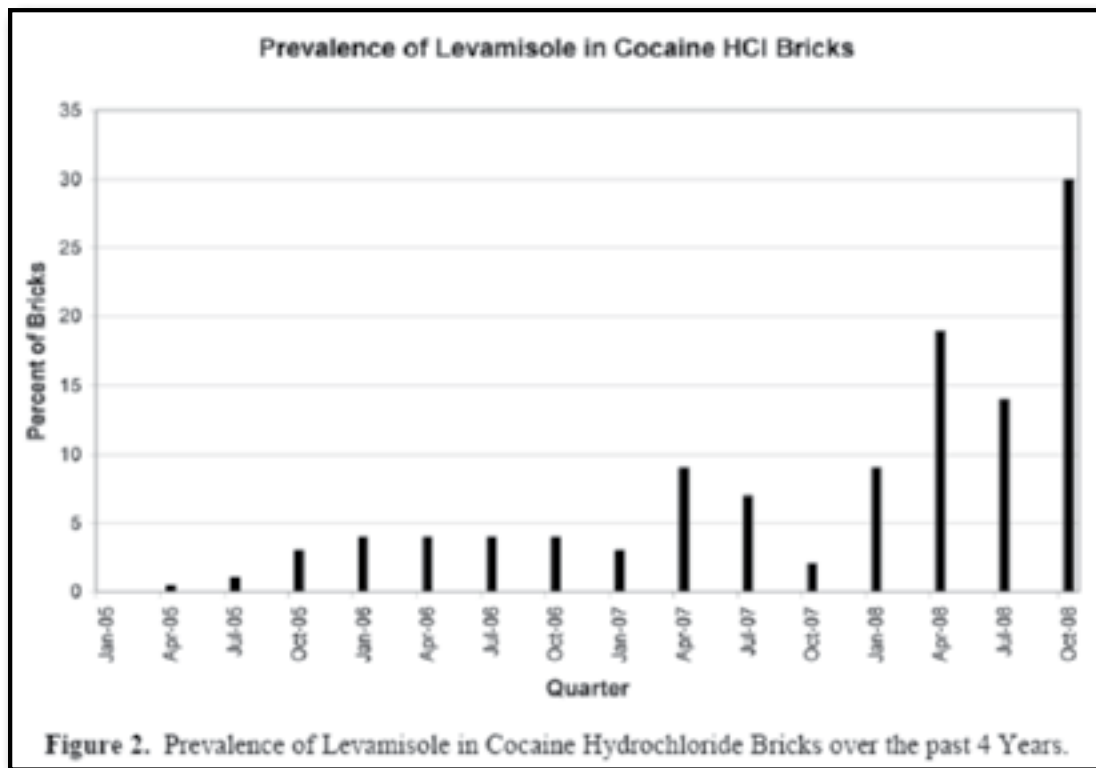
tal, lactose, lidocaine, diltiazem, etc.⁷. These serve simply as bulking agents or may be added because producers believe these substances will enhance the effects of or minimize the side effects of cocaine⁶. It is not clear, however, why a relatively expensive compound like levamisole would be chosen as an adulterant for cocaine.

One hypothesis is that levamisole is used to modulate neurotransmitter effect as an adjuvant to cocaine. This is supported by a study conducted by Spector and colleagues on the ability of levamisole to affect endogenous opiates⁸. This work was based on the extensive body of research conducted earlier by this group of investigators, as well as others, which identified morphine and codeine-like compounds in various tissues of several animal species, such as lower animals and mammals, including primates after levamisole use⁸⁻¹³. In addition, there is at least one report of these compounds in human tissues, specifically CSF¹². The role of these endogenous opiate alkaloids is not completely understood. But the above mentioned studies offer some theories.

For example, Oka et al⁹ isolated morphine-like compound (MLC) in the toad skin. They hypothesized that this compound is of endogenous origin, and not from a dietary source, as was proposed by other researchers, since skin was the only organ with detectable MLC concentration. They also theorized that morphine may serve in the regulation of the body temperature of this type of animal because it causes cutaneous vasodilatation⁹. Neri et al concluded that these endogenous opiate alkaloids may function as neuromodulators/ neurotransmitters in CNS of non human primates¹³.

In addition, detection of morphine precursors such as reticuline, salutaridine, thebaine, and codeine lead Spector et al, as well as other researchers, to believe that animal tissues are able to synthesize morphine from antecedent compounds^{9,13}. Weitz et al demonstrated the conversion in vivo and vitro of reticuline to salutaridine, a critical step that creates the morphine skeleton structure by rat liver. They hypothesized that this conversion is catalyzed by a specific enzyme, strengthening the argument for the endogenous origin of these MLCs¹⁰.

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The U.S. Drug Enforcement Agency reports that some cocaine originating from Colombian laboratories has been cut with pharmaceutical grade (pure) levamisole since 2003¹⁸. However, in January of 2008 DEA received a sample of "crack" cocaine for analysis that contained unknown impurities in addition to levamisole. Analysis revealed a presence of two degradation products of levamisole: 6-phenyl-2,3-dihydroimidazo[2,1b]thiazole (about 50% relative to levamisole content) and a trace amount of

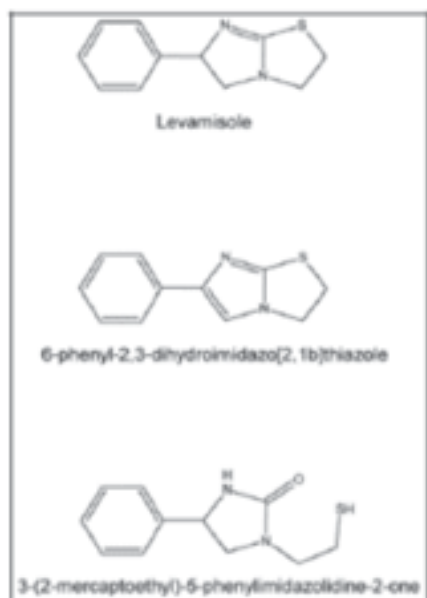


Figure 1.

(Ref 18)

tainted product^{6, 16-18}. This drug has an extensive list of side effects such as: nausea, vomiting, diarrhea, anorexia, stomach pains, mouth sores, muscle aches, fatigue, dizziness, headache, skin rashes³. The most disturbing side effects are those affecting the immune system: agranulocytosis, leucopenia, and thrombocytopenia, leading to life-threatening infections³. Zhu et al⁶ described 5 cases in Alberta, Canada, of cocaine abusers who were hospitalized for agranulocytosis, fever, and variety of infections complications. A newsletter of the Alberta Health Services of Canada, reports 39 cases (11 confirmed and 28 probable) of levamisole-associated neutropenia in cocaine users as of March 31st 2009¹⁹.

Levamisole exposure in cocaine abusers presenting with unexplained immunosuppressive symptoms is not likely to be confirmed via routine toxicology screening due to its short elimination half-life (0.5-2 hours in the plasma, and about 5.6 hours in the urine)^{6,17}. However, Zhu et al and Morley et al report some success with gas chromatography/mass spectrometry (GC/MS) assay and lupus anticoagulant testing^{6,17}.

In conclusion, the prevalence of levamisole in the cocaine supply is on the rise. The reason for its addition remains unknown. However, adulteration may be driven by producers' beliefs that levamisole increases the pharmacological effects of cocaine via its dopamine elevating properties. Clinicians should be on the alert for unusual symptoms in cocaine abusers that may not be attributed to the drug itself or other health conditions. These patient cases should be reported to their regional Poison Control Centers. In addition, confirmatory testing for levamisole is complicated and may not be readily available, making a definitive diagnosis difficult. To complicate the issue further, impurities in the levamisole added to the cocaine may become more prevalent, and their physiological effects are unknown.

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