HYDROXOCOBALAMIN FOR POISONING CAUSED BY INGESTION OF POTASSIUM CYANIDE: A CASE STUDY

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Abstract—Hydroxocobalamin, a precursor of vitamin B12, has a history of use in the prehospital setting in France for cyanide poisoning, particularly that associated with smoke inhalation. Because cyanide poisoning by ingestion is less common than smoke inhalation-associated cyanide poisoning, less information is available on prehospital use of hydroxocobalamin to treat cyanide poisoning by ingestion. This report describes a case of prehospital use of hydroxocobalamin for poisoning by ingestion of cyanide. The case supports the efficacy of hydroxocobalamin for acute cyanide poisoning caused by ingestion of a cyanide salt. No adverse events attributed to hydroxocobalamin were observed. © 2010 Elsevier Inc.

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INTRODUCTION

Cyanide poisoning is often rapidly lethal if it is not treated aggressively (1). Antidotal treatment can be life-saving. In the United States, the only currently approved cyanide antidote is a kit of amyl nitrite, sodium nitrite, and sodium thiosulfate (the Cyanide Antidote Kit [CAK]). Although this antidote is effective, it lacks a good risk:benefit ratio, particularly for empiric prehospital treatment when a diagnosis is uncertain (1). The nitrites induce methemoglobinemia, which can exacerbate ischemia in patients with low cardiopulmonary reserve, and can be harmful or fatal in smoke-inhalation victims with pre-existing anoxia secondary to carbon monoxide poisoning (1–5). In addition, the nitrites cause potent vasodilatation that can lead to hypotension and shock (3). As the sodium thiosulfate component of the CAK is limited by its slow onset of action, its use as a single antidote is suboptimal (6,7).

Another cyanide antidote, the vitamin B12 precursor hydroxocobalamin (Cyanokit®; Merck Santé S.A.S., Semoy, France), has been used in the prehospital and hospital settings in France since the 1980s and has recently been introduced in the United States. One use of hydroxocobalamin in France is prehospital treatment of cyanide poisoning caused by smoke inhalation, the most common cause of cyanide toxicity. In prospective and retrospective assessments of the prehospital use of hydroxocobalamin for suspected cyanide poisoning from smoke inhalation, antidotal treatment was well tolerated and associated with survival in the majority of patients (8,9). Less information is available on the use of hydroxocobalamin for cyanide poisoning arising from causes other than smoke inhalation. This article describes a case of prehospital use of hydroxocobalamin for poisoning caused by ingestion of cyanide.

CASE REPORT

Presentation

A 48-year-old man employed as a biochemical engineer was found comatose by his wife in the garden of the family house at 8:10 a.m., about 10 min after he was later deter-
mined to have ingested approximately 25 g of potassium cyanide. The patient was first examined and medical care was initiated upon arrival of the Paris Fire Brigade at the scene at approximately 8:15 a.m. The Paris Fire Brigade’s mobile intensive care units, with the Service d’Aide Médicale Urgente, provide the first line of prehospital care to victims of emergencies in Paris and its environs.

Upon initial evaluation, the patient was comatose (Glasgow Coma Score 3) and gasping for breath. His breath smelled of bitter almonds. Blood pressure was 160/80 mm Hg, and pulse was 130 beats/min.

**Prehospital Medical Care**

An intravenous line was immediately established, and blood samples were taken for later measurement of cyanide concentrations. Hydroxocobalamin (5 g × 2 for a total of 10 g) was infused intravenously beginning between 8:15 and 8:45 a.m. The patient was intubated and sedated with midazolam at 8:45 a.m., after three attempts. The intubation was difficult due to the patient’s short neck and the high anatomical position of the glottis.

During transport to the hospital, the patient showed signs of waking after hydroxocobalamin treatment. Therefore, continuous sedation (midazolam 9 mg/h and continuous analgesia with fentanyl 150 μg/h) was required.

**Clinical Course**

**Prehospital observations.** Hemodynamic parameters stabilized during and after treatment with hydroxocobalamin, as shown by blood pressure and pulse readings taken before arrival at the hospital (Table 1). Glasgow Coma Score remained at 3 during prehospital care because the patient was intubated and sedated with midazolam.

The first electrocardiogram (ECG) obtained at 8:41 a.m. showed subshifting of the ST segment in leads aVF and V1 through V6 (Figure 1)—a finding suggesting global myocardial injury. A second ECG obtained at 8:54 a.m. showed ventricular extrasystoles (Figure 1).

No adverse events attributed to hydroxocobalamin were observed. No discoloration of the skin or mucous membranes was observed after infusion of hydroxocobalamin.

**Observations during hospital care.** The patient was hospitalized in the Intensive Care Unit (ICU) at Percy Military Hospital in Clamart, France. The first ECG obtained in the ICU (at 2:06 p.m., approximately 6 h after ingestion of potassium cyanide) was normal, with no evidence of dysrhythmia (Figure 1). However, the acute myocardial injury suggested by prehospital ECGs was confirmed in the ICU by a high cardiac troponin concentration (0.27 μg).

Metabolic acidosis was present on the day of poisoning (Table 2). The first measured plasma arterial lactate concentration at 10:47 a.m., approximately 2 h after ingestion of potassium cyanide, was 5.0 mmol/L (the normal range for arterial plasma lactate concentration is 0.5–1.6 mmol/L.) Arterial pH and plasma arterial lactate concentration normalized over the ensuing 2 days (Table 2).

On the 3rd day of hospitalization, the patient was extubated. On the 6th day after ingestion of cyanide, the patient was discharged from the ICU for admission to the psychiatric department (due to his suicide attempt) with no neurological or other sequelae. The patient was admitted to the psychiatric department.

**Blood Cyanide Concentration**

Cyanide poisoning was confirmed a posteriori. Blood cyanide concentration determined from samples taken immediately upon establishment of the intravenous line and before administration of hydroxocobalamin was 3.64 mg/L, or 134.93 μmol/L. The threshold for cyanide poisoning is 1 mg/L, or ≥ 39 μmol/L (10). Concentrations exceeding 3.0 mg/L are frequently lethal.

| Table 1. Evolution of Hemodynamic Parameters after Infusion of Hydroxocobalamin |
|----------------------------------|---------|---------|---------|---------|---------|---------|---------|
| Hour (a.m.)                      |         |         |         |         |         |         |         |
|                                 | 8:15    | 8:30    | 8:45    | 9:00    | 9:15    | 9:30    | 9:45    |
| Glasgow Coma Score              |         |         |         |         |         |         |         |
|                                 | 3       | 3       | 3       | 3       | 3       | 3       | 3       |
| Pulse, beats/min                | 130     | 120     | 110     | 110     | 93      | 100     | 90      |
| Systolic blood pressure, mm Hg  | 160     | 160     | 150     | 140     | 160     | 140     | 140     |
| Diastolic blood pressure, mm Hg | 80      | 80      | 80      | 80      | 80      | 80      | 80      |
| Median arterial pressure, mm Hg | 107     | 107     | 103     | 100     | 107     | 100     | 100     |
| Arterial oxygen saturation, %   | 90      | 100     | 100     | 94      | 93      | 97      | 95      |
| Hydroxocobalamin administration, g | 2.5   | 2.5     | 2.5     | 2.5     | 2.5     | 2.5     | 2.5     |
DISCUSSION

This case supports the antidotal efficacy of hydroxocobalamin for acute cyanide poisoning caused by ingestion of a cyanide salt. Minutes after the patient ingested approximately 25 g potassium cyanide, pre-antidotal blood cyanide concentration was determined a posteriori to have been 3.64 mg/L, a value substantially exceeding the toxic and lethal thresholds of 1.0 mg/L and 3.0 mg/L, respectively. The high blood cyanide concentration, the patient’s respiratory distress and comatose state minutes after cyanide ingestion, and the electrocardiographic and

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<th>Table 2. Arterial pH and Arterial Lactate</th>
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<td>Day of Poisoning</td>
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enzymatic evidence of myocardial injury are consistent with the possibility that death would have ensued rapidly without intervention. Hydroxocobalamin administration beginning between 15 and 30 min after cyanide ingestion to a total dose of 10 g was associated with rapid stabilization of hemodynamic parameters and recovery of consciousness, and the patient was discharged from Intensive Care 6 days after the poisoning with no neurological or other sequelae.

This case supplements other reports of use of hydroxocobalamin for acute cyanide poisoning from ingestion or exposure to cyanide gas (11–14). In a recently reported case, hydroxocobalamin 5 g with supportive care was administered to a comatose 51-year-old man beginning 2.5 h after he attempted suicide by drinking a potassium cyanide solution (13). The patient could obey verbal orders within minutes of hydroxocobalamin infusion, and was discharged from the hospital with no neurological deficits on the 5th day after cyanide ingestion. A similarly rapid recovery was observed in a 68-year-old woman given hydroxocobalamin for suspected cyanide poisoning from ingestion of amygdalin and vitamin C (14). In a case series reported from the Hôpital Fernand Widal in France, 6 of 9 patients survived poisoning from ingestion of cyanide salts (n = 7), ingestion of acetonitrile (n = 1), or exposure to cyanogen bromide gas (n = 1) after administration of hydroxocobalamin (average dose 8.1 g, range 5–15 g) in the Emergency Department (11). Before hydroxocobalamin treatment, 5 of the patients were comatose, 6 were in shock, and 3 were in cardiorespiratory arrest. All 3 patients who died had been admitted several hours after the onset of cyanide intoxication and when neurologic impairment appeared to be irreversible. Considered in aggregate, these cases and data from prospective and retrospective studies of hydroxocobalamin for smoke inhalation-associated cyanide poisoning support the usefulness of hydroxocobalamin in the prehospital and hospital settings (8,9).

In the current case and in other reported uses of hydroxocobalamin, the antidote was administered empirically in the prehospital setting for suspected cyanide poisoning before a diagnosis could be confirmed via measurement of blood cyanide concentration. Empiric prehospital treatment of cyanide poisoning is often necessary to maximize the probability of successful intervention in the context of rapid progression of cyanide intoxication to serious toxicity and death. For empiric prehospital antidotal treatment to be practicable, the risk of introducing harm by administering the antidote should be low regardless of whether the presumptive diagnosis of cyanide poisoning is correct. Hydroxocobalamin administered in the prehospital setting for presumptive cyanide poisoning was not associated with adverse events in the current case or in other studies (8,9,11–14).

Unlike the CAK, hydroxocobalamin does not reduce the ability of the blood to carry oxygen or seem to cause hemodynamic instability. In previous investigations, hydroxocobalamin was associated with discoloration of the mucous membranes, skin, and urine, and interference with specific colorimetric clinical laboratory values, including aspartate aminotransferase, total bilirubin, creatinine, and magnesium (15,16). Both effects, attributed to the red color of the hydroxocobalamin molecule, are transient and not considered to be clinically significant. Red discoloration of the skin and mucous membranes was not observed during prehospital care in the patient treated in this case, and colorimetric laboratory values were not assessed for possible effects of hydroxocobalamin. Use of hydroxocobalamin has also been associated with allergic responses and anaphylactic reactions, which seem to occur very rarely (17–19). Allergic reactions to hydroxocobalamin are manifested by chest tightness, edema, urticaria, pruritus, dyspnea, and rash. The information available to date suggests that hydroxocobalamin has tolerability and safety profiles rendering it suitable for prehospital treatment of suspected cyanide poisoning.

Humanistic and ethical considerations prevent assessment of the clinical efficacy and tolerability of cyanide antidotes under double-blind or placebo-controlled conditions. Instead, evidence of the effectiveness and tolerability of antidotes comes from observational, “real-world” assessments including case reports such as this one. The uncontrolled nature of these assessments does not allow definitive attribution of clinical success to hydroxocobalamin. Given the lack of hypotension, the mild and prolonged acidosis, the prompt medical care, and ventilation in the field, it is possible that the patient would have survived without having received hydroxocobalamin. These considerations notwithstanding, the evidence considered in aggregate shows hydroxocobalamin to have a risk:benefit ratio making it potentially useful in both the prehospital and hospital settings.

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REFERENCES