# Prospective Study of Hydroxocobalamin for Acute Cyanide Poisoning in Smoke Inhalation

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**Study objective:** To assess outcomes in patients treated with hydroxocobalamin at the fire scene or in the ICU for suspected smoke inhalation-associated cyanide poisoning.

**Methods:** Adult smoke inhalation victims with suspected cyanide poisoning as determined by soot in the face, mouth, or nose or expectorations and neurologic impairment received an intravenous infusion of hydroxocobalamin 5 g (maximum 15 g) at the fire scene or in the ICU in this observational case series conducted from 1987 to 1994. Blood cyanide specimens were collected before administration of hydroxocobalamin. The threshold for cyanide toxicity was predefined as greater than or equal to 39 $\mu$mol/L.

**Results:** The sample included 69 patients (mean age 49.6 years; 33 men), of whom 39 were comatose. Out-of-hospital deaths were excluded. Fifty of the 69 patients (72%) admitted to the ICU survived after administration of hydroxocobalamin. In the group in which cyanide poisoning was confirmed a posteriori (n=42), 67% (28/42) survived after administration of hydroxocobalamin. The most common adverse events were chromaturia (n=6), pink or red skin discoloration (n=4), hypertension (n=3), erythema (n=2), and increased blood pressure (n=2). No serious adverse events were attributed to hydroxocobalamin. Laboratory tests revealed transient alterations in renal and hepatic function consistent with the critical condition of the patients and mild anemia consistent with progressive hemodilution.

**Conclusion:** Empiric administration of hydroxocobalamin was associated with survival among 67% of patients confirmed a posteriori to have had cyanide poisoning. Hydroxocobalamin was well tolerated irrespective of the presence of cyanide poisoning. Hydroxocobalamin appears to be safe for the out-of-hospital treatment of presumptive cyanide poisoning from smoke inhalation. [Ann Emerg Med. 2007;49:794-801.]

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**SEE EDITORIAL, P. 814.**

## INTRODUCTION

### Background

Inhalation of smoke accounts for more fire-related morbidity and mortality than burns.[1,2] Hydrogen cyanide contributes significantly to smoke inhalation deaths and injuries and is the most common cause of acute cyanide poisoning in developed countries.[3-6] Treatment of acute cyanide poisoning entails supportive care and the administration of an antidote.[7,8] The ability to administer an antidote empirically outside of the hospital for presumptive cyanide poisoning allows for early intervention that can be lifesaving. The potential for serious adverse effects limits or prevents the use of some currently available cyanide antidotes as out-of-hospital empiric treatment, particularly for cyanide poisoning caused by smoke inhalation. Both 4-dimethylaminophenol (4-DMAP) and the cyanide antidote kit (consisting of amyl nitrite, sodium nitrite, and sodium thiosulfate) are generally considered unsuitable for out-of-hospital use in smoke inhalation victims because of the presence of hypoxemia of multiple causes, including concomitant carbon monoxide poisoning.[4,9-12] The cyanide antidote kit and DMAP cause methemoglobinemia, which is potentially detrimental because it can further reduce the

**Editor's Capsule Summary**

*What is already known on this topic*

Intravenous hydroxocobalamin was well tolerated in small safety studies of healthy human volunteers and has been efficacious in reversing cyanide toxicity in animals.

*What question this study addressed*

Can hydroxocobalamin be safely administered to critically ill smoke inhalation victims suspected of having cyanide poisoning?

*What this study adds to our knowledge*

In this prospective case study of 69 smoke inhalation victims, out-of-hospital administration of hydroxocobalamin was well tolerated. Adverse effects were uncommon and benign.

*How this might change clinical practice*

Hydroxocobalamin has recently been approved for the treatment of cyanide poisoning. This small study suggests, but does not prove, that the drug is safe when administered to critically ill smoke inhalation victims. Its effectiveness in undifferentiated smoke inhalation patients is yet to be determined.

oxygen-carrying capacity of the blood. Although sodium thiosulfate can be used alone for suspected smoke inhalation cyanide poisoning, this component of the cyanide antidote kit is thought to have a relatively slow onset of action[8] and has not been prospectively studied in the context of smoke inhalation.

### Importance

The cyanide antidote hydroxocobalamin has been used regularly in France for out-of-hospital and inhospital treatment of cyanide poisoning since the 1980s and was formally licensed there in 1996. A natural form of vitamin $B_{12}$, hydroxocobalamin detoxifies cyanide through the irreversible formation of cyanocobalamin, which is subsequently excreted in urine. Successful use of hydroxocobalamin for out-of-hospital and inhospital treatment of acute cyanide poisoning from smoke inhalation, ingestion, and occupational exposure has been documented in case reports and series,[13-19] but data from prospective studies have not been reported to date.

### Goals of This Investigation

This study was conducted to assess outcomes in patients treated with hydroxocobalamin in the out-of-hospital setting or ICU for smoke-inhalation-associated cyanide poisoning.

## MATERIALS AND METHODS

### Study Design and Setting

This study was conducted in Paris, France, among fire victims initially treated by members of the Paris Fire Brigade for presumptive smoke inhalation-induced cyanide poisoning. The Paris Fire Brigade operates an out-of-hospital emergency medical service composed of 7 mobile ICUs staffed at any given time by a physician, nurse, and driver. The brigade is responsible for providing emergency medical services to Paris and its environs, totaling a 759-$km^2$ area of 6,188,434 inhabitants (according to the 2002 census). In concert with the Service d'Aide Médicale Urgente, the Paris Fire Brigade provides the first line of out-of-hospital emergency care to victims of fires and other emergencies. All patients entered into this study were admitted to the Toxicological Intensive Care Unit at Fernand Widal Hospital.

The study was a prospective, observational case series. An active control group was not included because of the lack of a safe alternative cyanide antidote in France. A placebo control group was not included because it was not considered ethical to withhold potentially lifesaving antidotal treatment from patients assigned to placebo. The study was conducted in accordance with the Declaration of Helsinki and with standards of good clinical practice as defined by the European Community. The ethics committee of the Assistance Publique–Hôpitaux de Paris approved the protocol.

### Selection of Participants

Smoke inhalation victims who were examined at the fire scene by a physician of the Paris Fire Brigade from June 1987 through February 1994 were eligible for the study if they were older than 15 years; had soot in the mouth, nose, or expectorations; had altered neurologic status as reflected by altered mental status or disturbance of consciousness; and were admitted to the Toxicology Intensive Care Unit of the Fernand Widal Hospital. Altered mental status included agitation, slowed ideation, or mental confusion; disturbance of consciousness was assessed with the Glasgow Coma Scale. All patients surviving to the hospital were admitted to the Toxicology Intensive Care Unit except those dead at the scene. Those excluded were women who were obviously pregnant; individuals found with burns on the face and neck or with greater than or equal to second-degree burns involving greater than 20% of the total body surface area as determined by a critical care physician or a burn specialist; and individuals with obvious external multiple trauma. The requirement for informed consent was waived because of the need to administer care immediately to patients who were in critical condition and who were often unable to provide informed consent.

### Data Collection and Processing

Eligible patients were identified and enrolled at the fire scene by a physician member of the Paris Fire Brigade. After initial examination by the physician, oxygen was administered by a nonrebreather mask or, if warranted, by mechanical ventilation with a bag-valve-mask device, followed by endotracheal intubation. An intravenous catheter was placed, and blood samples (5 mL over heparin in a dry, closed tube) were obtained for analyses of cyanide and carbon monoxide concentrations.

As soon as was practicable after the initial blood draw, hydroxocobalamin (5 g; supplied by the Pharmacie Centrale des Hôpitaux, Assistance Publique–Hôpitaux de Paris as a 5% weight/volume solution in 100 mL sterile water for injection) was infused intravenously during 15 to 30 minutes. Additional doses of hydroxocobalamin could be administered to a maximum of 15 g at the discretion of the treating physician for incomplete hemodynamic or neurologic response to treatment at the fire scene or on arrival at the Toxicology Intensive Care Unit of the Fernand Widal Hospital, where victims were transferred by ambulance. Supportive therapy (eg, volume replacement, catecholamines, assisted ventilation, hyperbaric oxygen therapy) was administered according to need and at the discretion of the treating physician.

**Outcome Measures**

Posttreatment hospital outcomes were assessed for patients admitted to the ICU. Measures included (1) blood cyanide and carbon monoxide concentrations before administration of hydroxocobalamin; (2) pulse rate, systolic and diastolic blood pressure, and neurologic status (amelioration of neurologic signs) assessed immediately before antidote infusion, at the end of the antidote infusion, and on arrival at the ICU; (3) results of standard clinical chemistry and hematology laboratory tests (electrolytes, liver and kidney function tests, differentiated blood cell count, prothrombin, lactate) on blood samples drawn on arrival at the ICU (day 0) and on each of the first 3 days of hospitalization (days 1 to 3); and (4) adverse events, defined as a side effect the treating physician judged to be at least potentially attributed to hydroxocobalamin. Amelioration of neurologic signs included diminution of agitation, mental confusion, and slowness of ideation for altered mental status; improvement in disturbance of consciousness was assessed by change in the Glasgow Coma Scale score. Adverse event data were collected on a data collection form, with check boxes for the following adverse events of special interest: rash, urticaria, anaphylactic shock, bronchoconstriction, and Quincke's edema. The data collection form included a blank box for recording additional adverse events not included on the check-box list. A comprehensive supplemental medical record review was performed before article submission for data quality assurance. The record review of adverse events was intended to identify any adverse events that were not originally coded as such. Hospital records were obtained from the medical records archives at Fernand Widal Hospital. Documents reviewed included, where available, the out-of-hospital record of treatment by the Paris Fire Brigade and the ICU flow sheet, which shows all vital signs, treatments, and medications administered. The physician's admitting notes, progress notes, and nursing notes were used to supplement or clarify entries and to document the occurrence of adverse events. The data were collected on a standardized data sheet designed for this purpose and then transferred to a database.

Presence of neuropsychiatric sequelae was also assessed. Neuropsychiatric sequelae were defined as abnormal persistent neuropsychiatric signs or symptoms present at hospital discharge among patients with no history of such signs or symptoms. There was no long-term, postdischarge follow-up of patients to assess neuropsychiatric sequelae.

Blood samples were stored for up to 90 minutes at ambient temperature during transport and then stored for no longer than 3 days at 4°C (39.2°F) until the assays (including standard clinical chemistry and hematology tests, carbon monoxide, cyanide, and plasma lactate) were performed by hospital laboratory technicians. Previous studies on the effects of duration of storage of blood samples on carbon monoxide and cyanide concentrations showed limited effects for cyanide and no effects for carbon monoxide at the duration of storage used in the present study.[6,20] Plasma lactate was measured using the Marbach and Weil enzymatic method.[21] In the context of smoke inhalation, plasma lactate level greater than or equal to 10 mmol/L has been shown to be a sensitive and specific marker of cyanide poisoning, defined as a blood concentration of cyanide greater than or equal to 39 μmol/L, or approximately 1 mg/L.[6] Carbon monoxide can also cause lactic acidosis that is typically much less severe than that associated with cyanide.[22]

Blood cyanide was determined with a colorimetric assay using microdiffusion.[23] The detection threshold was 2.2 μmol/L, and the interassay coefficient of variation was 8%. A value of zero was assigned to blood samples with cyanide concentrations below the threshold of detection. Thresholds for toxic and potentially lethal blood cyanide concentrations were defined as 39 μmol/L (≈1 mg/L) and 100 μmol/L (≈2.7 mg/L), respectively.[6]

Blood carbon monoxide concentrations were measured by infrared analysis.[24] Thresholds for elevated and potentially lethal blood concentrations of carbon monoxide were defined as 1.0 and 5.8 mmol/L, respectively. According to the Pace et al[25] approximation, 1 mmol/L of carbon monoxide in blood corresponds to 11% of carboxyhemoglobin in a person with a normal hemoglobin value.

**Primary Data Analysis**

Data were summarized descriptively for the sample as a whole, the subgroups of patients defined by cyanide poisoning status (cyanide-poisoned, blood concentration ≥39 μmol/L; not cyanide-poisoned, blood concentration <39 μmol/L), and the subgroups of patients defined by cardiorespiratory status (found in cardiorespiratory arrest, not found in cardiorespiratory arrest). No hypothesis testing was undertaken.

## RESULTS

The sample included 69 patients (36 women and 33 men; median age 44 years [range 20 to 94 years]) (Table 1). All patients were victims of house fires in Paris or its environs and were subsequently admitted to the Toxicology Intensive Care Unit of the Fernand Widal Hospital. Mean (SD) time between the initial call for help and initiation of out-of-hospital care was 10.4 minutes (6.2 minutes). Fifteen victims who were examined at the fire scene by the Paris Fire Brigade and treated with hydroxocobalamin were not included in the study sample, because they did not meet these entry criteria (age <15 years

**Table 1.** Baseline clinical characteristics and blood cyanide and carbon monoxide concentrations.

| Characteristic | Value |
|---|---|
| N | 69 |
| **Demography** | |
| **Sex, No.** | |
| Female | 36 |
| Male | 33 |
| Mean age, y (SD) | 49.6 (20) |
| Median age, y (range) | 44 (20–94) |
| **Clinical status** | |
| Neurologic impairment present, No. (%) | 66 (96) |
| Coma, No. | 39 |
| **Altered mental status,* No.** | |
| Agitation | 14 |
| Confusion | 13 |
| Slowed ideation | 12 |
| Initial cardiorespiratory arrest present, No. (%) | 15 (22) |
| **Pretreatment blood cyanide data†** | |
| **Cyanide poisoning status, No. (among 63 patients with samples)** | |
| Present (cyanide concentration ≥39 μmol/L) | 42 |
| Absent (cyanide concentration <39 μmol/L) | 21 |
| **Median cyanide concentration, μmol/L (25th, 75th percentile)** | |
| All patients (n=63) | 52.0 (0, 250) |
| **By cyanide poisoning status** | |
| Present (n=42) | 96 (40, 250) |
| Absent (n=21) | 8 (0, 27) |
| **By initial cardiorespiratory status** | |
| Cardiorespiratory arrest present (n=13) | 123 (0, 239) |
| Cardiorespiratory arrest absent (n=50) | 45 (0, 250) |
| **Pretreatment blood carbon monoxide data** | |
| **Carbon monoxide poisoning status, No. (among 69 patients with samples)** | |
| Present (carbon monoxide concentration ≥1 mmol/L) | 57 |
| Absent (carbon monoxide concentration <1 mmol/L) | 12 |
| **Median carbon monoxide concentration, mmol/L (25th, 75th percentile)** | |
| All patients (n=63) | 2.4 (1.3, 3.8) |
| **By cyanide poisoning status** | |
| Present (n=42) | 2.9 (2.1, 4.1) |
| Absent (n=21) | 1.6 (1.1, 2.6) |
| **By initial cardiorespiratory status** | |
| Cardiorespiratory arrest present (n=15) | 2.7 (2.1, 4.6) |
| Cardiorespiratory arrest absent (n=54) | 2.2 (1.2, 3.8) |

*Patients could have more than 1 manifestation of altered mental status.
†According to Pace's[25] approximation, 1 mmol/L of carbon monoxide in blood corresponds to 11% of carboxyhemoglobin in a person with a normal hemoglobin value.

[n=6], burns on the face and neck or with ≥second-degree burns of >20% of the body surface [n=6], patient not victim of a structural fire [self-ignition of benzene on clothes in a suicide attempt] [n=1], incomplete documentation [n=2]). No hospitalized patient was subsequently found to have undetected significant traumatic injuries. Some of these patients died at the scene, and documentation of outcome is unavailable for others; therefore, overall survival figures cannot be calculated in this study according to total numbers treated with hydroxocobalamin at the scene.

The number of patients known to have received hyperbaric oxygen therapy was 57. For the remaining 12 patients, hyperbaric oxygen was either not given (n=9) or status with respect to hyperbaric oxygen therapy was not known (n=3). Among the 63 patients with blood cyanide concentrations available, hyperbaric oxygen therapy was given to 52 patients, 18 with blood cyanide level less than 39 μmol/L and 34 with blood cyanide greater than or equal to 39 μmol/L.

All patients had soot particles in the mouth or upper airways. All but 3 patients (66 of 69) had neurologic impairment. Thus, the sample included 3 patients who, in violation of eligibility criteria, were neurologically intact or had neurologic data missing but who otherwise met eligibility criteria. Of the 66 neurologically impaired patients, 39 were in a coma. Fifteen (15) of 69 patients (22%) were found in cardiorespiratory arrest. Data for all study endpoints were analyzed both for the intent-to-treat population (n=69) and the subsample who were neurologically impaired at baseline (n=66). The results did not differ appreciably between the intent-to-treat population and the subsample with neurologic impairment at baseline for any endpoint. Survival rates are reported below for both the intent-to-treat population and the neurologically impaired subsample; other endpoints reported below are based on the intent-to-treat population.

Blood cyanide and carbon monoxide concentrations were evaluable for 63 of the 69 patients. Blood samples were not obtained in the remaining 6 patients. For the sample as a whole, pretreatment median ($25^{th}$, $75^{th}$ percentiles) blood cyanide and carbon monoxide concentrations were 52.0 μmol/L (0, 250) and 2.4 mmol/L (1.3, 3.8), respectively. The presence of cyanide poisoning defined by a pretreatment blood cyanide concentration greater than or equal to 39 μmol/L was confirmed in 42 of the 63 patients with evaluable data (67%). The remainder of patients had blood cyanide concentrations less than 39 μmol/L (n=21; 33%). Nine of these 21 patients had undetectable blood cyanide concentrations. The median (range) blood cyanide concentration in the 21 patients with concentrations less than 39 μmol/L was 8.0 μmol/L (0 to 27 μmol/L). Median blood cyanide concentrations were higher among patients with initial cardiorespiratory arrest than patients without initial cardiorespiratory arrest (123.0 versus 45.0 μmol/L) (Table 1). In contrast, median blood carbon monoxide concentrations were comparable between these subgroups.

Of the 69 patients treated with hydroxocobalamin (median dose 5 g during a median infusion time of 30 minutes) and admitted to the Toxicology Intensive Care Unit of the Fernand Widal Hospital, 50 (72%) survived (Table 2). Among the 19 patients who died, the main cause of death was decerebration, occurring in 13 patients who had cardiac arrest at the scene; 3 of these 13 developed multiple organ failure. The remaining 6 fatalities, occurring long after the initial smoke exposure, were attributed to infectious complications (5 to septic shock, 1 to pneumonia).

Among the 66 patients with neurologic impairment before antidote administration, 47 (71%) survived and 19 died. Neurologic signs improved with no sequelae in 38 patients

**Table 2.** Clinical outcomes and hemodynamic measures.

| Clinical Outcomes and Hemodynamic Measures | All Patients (n=69) | Cyanide Poisoning Status | | Cardiorespiratory Status* | |
|---|---|---|---|---|---|
| | | Present (n=42) | Absent (n=21) | Arrest Present (n=15) | Arrest Absent (n=54) |
| **Survival rate** | | | | | |
| **Outcome, No. (%)** | | | | | |
| Survival | 50 (72) | 28 (67) | 18 (86) | 2 (13) | 48 (89) |
| Death | 19 (28) | 14 (33) | 3 (14) | 13 (87) | 6 (11) |
| Decerebration, No. | 13 | 9 | 2 | 13 | 0 |
| Septic shock, No. | 5 | 4 | 1 | 0 | 5 |
| Pneumonia, No. | 1 | 1 | 0 | 0 | 1 |
| **Neurologic outcomes** | | | | | |
| Initial neurologic signs present,† No. (%) | 66 (96) | 41 (98) | 19 (90) | 15 (100) | 51 (94) |
| **Neurologic outcome, No. (%)** | | | | | |
| Resolution | 38 (58) | 21 (51) | 13 (68) | 2 (13) | 36 (71) |
| Neuropsychiatric sequelae | 9 (14) | 6 (15) | 3 (16) | 0 (0) | 9 (18) |
| Death | 19 (29) | 14 (34) | 3 (16) | 13 (87) | 6 (12) |
| **Hemodynamic characteristics** | | | | | |
| **Median pulse rate, bpm (25th, 75th percentile)** | | | | | |
| Preinfusion | 98 (81, 109) | 96 (79, 104) | 100 (90, 115) | 0 (0, 80) | 100 (90, 110) |
| At the end of first infusion | 91 (80, 105) | 94 (84, 106) | 89 (79, 97) | 100 (81, 110) | 91 (80, 100) |
| On arrival at the ICU | 98 (80, 110) | 100 (80, 100) | 98 (81, 102) | 104 (80, 115) | 97 (80, 108) |
| **Median systolic blood pressure, mm Hg (25th, 75th percentile)** | | | | | |
| Preinfusion | 123 (100, 140) | 120 (90, 140) | 130 (120, 145) | 0 (0, 120) | 130 (112, 145) |
| At the end of first infusion | 140 (120, 150) | 140 (120, 150) | 130 (110, 150) | 130 (70, 150) | 140 (120, 150) |
| On arrival at the ICU | 125 (109, 150) | 125 (100, 150) | 132 (115, 145) | 120 (60, 150) | 125 (110, 150) |
| **Median diastolic blood pressure, mm Hg (25th, 75th percentile)** | | | | | |
| Preinfusion | 70 (60, 80) | 70 (60, 80) | 80 (65, 85) | 0 (0, 70) | 80 (70, 90) |
| At the end of first infusion | 80 (70, 87) | 80 (70, 80) | 79 (60, 85) | 70 (60, 80) | 80 (70, 90) |
| On arrival at the ICU | 80 (60, 100) | 80 (65, 90) | 90 (59, 102) | 70 (47, 90) | 80 (60, 100) |

*Patients might have received supportive treatment (eg, catecholamines, cardiopulmonary resuscitation) that explains the presence of a pulse rate and blood pressure at the preinfusion measurements in patients in cardiac or cardiorespiratory arrest.
†Neurologic outcomes were not known for all patients.

(58%). Neuropsychiatric sequelae were observed in 9 patients (14%) (Table 2). Persistent sequelae included confusion (n=2), memory impairment (n=2), cerebellar syndrome (n=2), psychomotor retardation (n=1), intellectual deterioration (n=1), dementia (n=1), and aphasia (n=1). (A patient could have more than 1 sequela.)

Hemodynamic parameters are shown in Table 2. The median difference between blood pressure values preinfusion and at the end of the first infusion was +10.0 mm Hg (range –60 to 160 mm Hg) for systolic and +7.5 mm Hg (range –30 to 90 mm Hg) for diastolic.

Of the 42 patients with confirmed cyanide poisoning, 28 (67%) survived after treatment with hydroxocobalamin (Table 2). The percentages of patients who survived with initial blood cyanide concentrations greater than or equal to 39 to 99 μmol/L and greater than or equal to 100 μmol/L were 74% (17 of 23) and 62% (8 of 13), respectively. Among patients having blood cyanide concentrations of at least twice the potentially lethal level (≥200 μmol/L), the survival rate was 50% (3 of 6).

Among the 14 patients with confirmed cyanide toxicity who died, the main cause of death was decerebration, occurring in 9 patients, including 2 with multiple organ failure. The remaining 5 fatalities, occurring long after the initial cyanide exposure, were attributed to infectious complications (4 to septic shock, 1 to pneumonia with multiple organ failure).

Forty-one of 42 of the patients with confirmed cyanide toxicity had neurologic impairment before antidote administration. Neurologic signs improved with no sequelae in 21 patients (51%). Neuropsychiatric sequelae were observed in 6 patients (15%) (Table 2).

Hemodynamic characteristics are shown in Table 2. The median difference between blood pressure values preinfusion and at the end of the first infusion in patients with confirmed cyanide toxicity was +15.0 mm Hg (range –60 to 160) for systolic and +10.0 mm Hg (range –20 to 90) for diastolic.

Of the 21 patients with blood cyanide concentrations less than 39 μmol/L, 18 (86%) survived and 3 died (Table 2). The main causes of death were decerebration and septic shock. Two of the 3 patients who died were initially found in cardiorespiratory arrest. Neurologic and hemodynamic outcomes for patients with blood cyanide concentrations less than 39 μmol/L are shown in Table 2.

Among the 15 patients found in cardiorespiratory arrest, median (25th, 75th percentile) blood cyanide concentration was

123 μmol/L (0, 239) (Table 1). Two of the 15 patients (13%) found in cardiac arrest survived after treatment with hydroxocobalamin (Table 2). The remaining 13 patients died of decerebration. Three of these 13 patients had concomitant multiple organ failure. All of the patients had severe neurologic impairment caused by cardiopulmonary arrest before antidote administration. The 2 patients who survived recovered neurologic function with no sequelae (Table 2).

Hemodynamic characteristics initially improved on administration of hydroxocobalamin to these patients found in cardiorespiratory arrest (Table 2). The median difference between blood pressure values preinfusion and at the end of the first infusion in patients found in cardiorespiratory arrest was +70.0 mm Hg (range –10 to 160) for systolic and +10.0 mm Hg (range 0 to 90) for diastolic.

Of the 54 patients not in cardiorespiratory arrest, 48 (89%) survived and 6 died (Table 2). Among the 51 patients with neurologic impairment, 36 recovered with no sequelae (Table 2). Pretreatment and posttreatment hemodynamic characteristics are shown in Table 2.

Of the 69 patients, 19 (27.5%) experienced at least 1 adverse event identified as possibly related to hydroxocobalamin. The most common adverse events were chromaturia (n=6), pink or red skin discoloration (n=4), hypertension (n=3), erythema (n=2), and increased blood pressure (n=2). (Because adverse events are listed as they were reported by the treating physician or checked on the data collection form, seemingly synonymous terms [eg, pink or red skin discoloration/erythema] could be used to characterize adverse events.) No other adverse events considered possibly related to hydroxocobalamin were reported in more than 1 patient. No allergic reactions were reported.

Plasma lactate level on admission to the ICU was obtained after hydroxocobalamin administration in some patients and before hydroxocobalamin administration in others. In the sample as a whole, median plasma lactate level on admission to the ICU was increased (Appendix E1, available online at http://www.annemergmed.com). Lactic acidemia improved during the first 3 days of hospitalization such that median plasma lactate was 2.0 mmol/L by day 3. A similar pattern of results, with substantially higher initial plasma lactate values on admission to the ICU, was observed in the subset of patients with confirmed cyanide poisoning and the subset with initial cardiorespiratory arrest (Appendix E1, available online at http://www.annemergmed.com).

Other clinical laboratory findings (Appendix E1, available online at http://www.annemergmed.com) were consistent with the critical condition of the sample of patients and with progressive hemodilution because of fluid repletion and repeated blood sampling during the 3-day inhospital study period. No findings were attributed to adverse effects of hydroxocobalamin. Laboratory tests revealed transient alterations in renal function and in hepatic function, as assessed by creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and prothrombin index. All patients were hyperglycemic on hospital admission. RBC counts, hemoglobin levels, and hematocrit values revealed a gradual development of anemia.

## LIMITATIONS

The data from this study should be interpreted in the context of several limitations that prevent making inferences about hydroxocobalamin efficacy. These limitations include the absence of a contemporaneous control group, the open-label design, and the impact of multiple other interventions administered around the time of hydroxocobalamin treatment. Caution should be exercised in the interpretation of outcome data because of the presence in fire smoke of multiple toxicants, including carbon monoxide. Nonetheless, cyanide appears to have a closer association than carbon monoxide with the presence of initial cardiac arrest. Moreover, information on factors such as the duration of smoke exposure and the time of smoke exposure relative to initiation of care was not available to contextualize the study findings. An additional limitation is the inability to obtain self-reports of adverse events from patients who were neurologically impaired.

## DISCUSSION

With a half-life of approximately 1 to 3 hours,[6,26,27] cyanide disappears rapidly from blood. Technologic and logistic limitations make it difficult to analyze blood from smoke-inhalation victims within the time required for accurate measurement of peak cyanide concentrations. Research that has overcome these impediments to measure cyanide in blood sampled close to the time of smoke exposure demonstrates the presence of cyanide at toxic to lethal levels in the blood of many individuals exposed to smoke in closed-space fires.[3] These previous findings are confirmed by results of the current prospective study in which cyanide was measured from blood samples collected from smoke inhalation victims at the scenes of house fires in Paris and its environs. Two thirds (67%; 42 of 63) of patients presenting with soot deposits and neurologic disturbances and for whom blood cyanide data were evaluable had confirmed cyanide poisoning, defined as a blood concentration greater than or equal to 39 μmol/L. Not surprisingly, significant carbon monoxide poisoning occurred concomitantly with cyanide poisoning.

Of the 69 patients in the study sample, 50 (72%) survived after treatment with hydroxocobalamin and admission to the Toxicology Intensive Care Unit of the Fernand Widal Hospital. Administration of hydroxocobalamin to patients treated for presumptive cyanide poisoning was associated with survival among 67% (28 of 42) of patients who were admitted to the ICU and were confirmed a posteriori on the basis of blood cyanide concentrations to have had cyanide poisoning. Outcomes in the subgroup of patients found in cardiorespiratory arrest were considerably poorer than those for the sample as a whole and those not found in cardiorespiratory arrest. The majority (13 of 15) of patients found in cardiorespiratory arrest died despite initial improvement in hemodynamic measurements after administration

of hydroxocobalamin. Given the inability of an antidote to correct severe cerebral hypoxia associated with cardiorespiratory arrest, the high fatality rate in this subgroup of patients is not unexpected.

Median values for systolic and diastolic blood pressure generally remained stable or increased modestly during and after hydroxocobalamin infusion in smoke inhalation victims found a posteriori not to have had cyanide poisoning. In smoke inhalation victims confirmed a posteriori to have had cyanide poisoning, administration of hydroxocobalamin was associated with an increase in blood pressure and improvement of hemodynamic status, effects observed even among patients who were found in cardiorespiratory arrest. The increase in blood pressure in cyanide-poisoned patients is consistent with the previous finding of transient, self-limiting increases in systolic and diastolic blood pressure in studies of hydroxocobalamin administered to healthy volunteers at doses ranging from 2.5 g to 10 g.[28,29] The mechanism of the effects of hydroxocobalamin on blood pressure is likely attributable to its ability to scavenge the vasodilator nitric oxide.[30,31] Together, data from healthy volunteers and cyanide-poisoned patients suggest that hydroxocobalamin-associated increases in blood pressure do not pose untoward risks in individuals without cyanide toxicity and may be beneficial in counteracting hypotension in cyanide-poisoned patients. The association of hydroxocobalamin infusion with the maintenance of hemodynamic stability in nonpoisoned patients and with improvement in hemodynamic status in cyanide-poisoned patients appears to differentiate it from other cyanide antidotes, including the cyanide antidote kit, dicobalt edetate, and 4-DMAP, all of which can compromise hemodynamic stability.[7,8,32] Although the observation of blood pressure increases in many patients in this study is consistent with the previous data linking hydroxocobalamin to such increases, numerous factors other than hydroxocobalamin could have contributed to blood pressure changes in this sample of critically ill patients. Examples include catecholamine administration and noxious stimuli, including airway suctioning, endotracheal intubation, intravenous line placement, and fluid resuscitation.

No serious adverse events attributed to hydroxocobalamin were reported in this study. Red coloration of the skin, the infused vein, and the urine were noted after hydroxocobalamin administration in many patients. This effect, which has been previously observed, is attributed to the red color of the hydroxocobalamin molecule.[9,29,33,34] In the current study, as in past investigations, the effect appeared not to be reason for clinical concern. Hydroxocobalamin also was not associated with clinically relevant changes in clinical laboratory tests in this study. Clinical laboratory results were consistent with the critical condition of the sample of patients and with progressive hemodilution because of fluid repletion and repeated blood sampling during the 3-day inhospital study period. Bilirubinemia was thought to be an artifact of administration of hydroxocobalamin, which because of its red color interferes with colorimetric laboratory tests.[33,34] The tolerability and safety profiles of hydroxocobalamin in the current investigation are consistent with previous results, including prospective investigations of healthy volunteers and smoke inhalation victims administered 5 g hydroxocobalamin.[13,14,28,29]

No allergic reactions associated with hydroxocobalamin were reported in this study. However, in other research, rare allergic reactions, including anaphylaxis, have been reported, primarily when hydroxocobalamin was used as long-term treatment for indications other than cyanide poisoning.[35,36] In addition, allergic reactions, including angioneurotic edema, have been reported in postmarketing experience with use of hydroxocobalamin as a cyanide antidote.[37] The occurrence in the aforementioned healthy volunteer study of 2 allergic reactions to hydroxocobalamin is consistent with these reports. In that study, the allergic reactions were successfully managed with standard treatment with a corticosteroid or antihistamine.[29]

The plasma lactate data in this study support previous findings suggesting that, in patients with smoke inhalation, concentrations of plasma lactate greater than or equal to 10 mmol/L are a relatively sensitive and specific marker of cyanide poisoning, defined as a blood cyanide concentration greater than or equal to 39 $\mu$mol/L.[6,26] Plasma lactate level normalized during the ensuing 3 days in cyanide-poisoned patients. Plasma lactate level on admission to the ICU was obtained after hydroxocobalamin administration in some patients and before hydroxocobalamin administration in others. Because hydroxocobalamin reduces lactic acidosis, the lactic acid values in this study should not be interpreted as reflecting the true nature and extent of cyanide-poisoning-associated lactic acidemia.

In conclusion, the results of this first prospective study of hydroxocobalamin for the out-of-hospital empiric treatment of smoke inhalation-associated cyanide poisoning suggest that the antidote is well tolerated both in smoke inhalation victims with cyanide poisoning confirmed a posteriori and in those found a posteriori not to have had cyanide poisoning. The safety data and the hemodynamic results suggest that hydroxocobalamin can be administered to smoke inhalation victims, including those with concomitant carbon monoxide poisoning, without introducing significant risk of harm. The safety profile of hydroxocobalamin allows it to be used empirically in the out-of-hospital setting for cases in which cyanide poisoning is suspected but cannot be confirmed within the short time available for initiating effective intervention.

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## APPENDIX E1.

Clinical laboratory data* (median values).

| | Day 0 | Day 1 | Day 2 | Day 3 |
|---|---|---|---|---|
| **Plasma lactate, mmol/L** | | | | |
| All patients (n=69) | 8.6 | 3.5 | 2.5 | 2.0 |
| Cyanide poisoning present (n=42) | 11.5 | 4.1 | 2.5 | 2.4 |
| Cyanide poisoning absent (n=21) | 6.1 | 2.2 | 2.1 | 1.8 |
| Cardiorespiratory arrest present (n=15) | 24.6 | 7.3 | 5.2 | 7.0 |
| Cardiorespiratory arrest absent (n=54) | 5.6 | 2.5 | 2.0 | 1.7 |
| **Creatinine, μmol/L** | | | | |
| All patients (n=69) | 81.0 | 75.0 | 73.0 | 69.0 |
| Cyanide poisoning present (n=42) | 89.5 | 81.0 | 71.5 | 69.0 |
| Cyanide poisoning absent (n=21) | 81.0 | 71.0 | 71.5 | 67.0 |
| Cardiorespiratory arrest present (n=15) | 115.0 | 142.0 | 151.5 | 93.0 |
| Cardiorespiratory arrest absent (n=54) | 72.5 | 72.0 | 68.0 | 65.0 |
| **Blood glucose, mmol/L** | | | | |
| All patients (n=69) | 10.7 | 8.5 | 7.6 | 7.6 |
| Cyanide poisoning present (n=42) | 12.5 | 8.8 | 7.6 | 8.1 |
| Cyanide poisoning absent (n=21) | 8.2 | 7.8 | 7.7 | 7.4 |
| Cardiorespiratory arrest present (n=15) | 21.0 | 14.7 | 7.1 | 8.5 |
| Cardiorespiratory arrest absent (n=54) | 10.0 | 8.1 | 7.6 | 7.4 |
| **Total bilirubin, μmol/L** | | | | |
| All patients (n=69) | 8.0 | 10.0 | 10.0 | 9.0 |
| Cyanide poisoning present (n=42) | 8.5 | 9.1 | 9.4 | 8.5 |
| Cyanide poisoning absent (n=21) | 6.5 | 15.8 | 11.3 | 10.0 |
| Cardiorespiratory arrest present (n=15) | 8.5 | 17.5 | 11.0 | — |
| Cardiorespiratory arrest absent (n=54) | 8.0 | 9.1 | 10.0 | 9.0 |
| **Alkaline phosphatase, IU/L** | | | | |
| All patients (n=69) | 81.0 | 64.0 | 65.5 | 63.5 |
| Cyanide poisoning present (n=42) | 81.5 | 64.0 | 60.0 | 59.0 |
| Cyanide poisoning absent (n=21) | 75.0 | 71.5 | 65.0 | 64.0 |
| Cardiorespiratory arrest present (n=15) | 86.0 | 57.0 | 57.0 | 63.0 |
| Cardiorespiratory arrest absent (n=54) | 81.0 | 65.0 | 66.0 | 64.0 |
| **Aspartate aminotransferase (AST), IU/L** | | | | |
| All patients (n=69) | 34.0 | 36.0 | 35.5 | 37.5 |
| Cyanide poisoning present (n=42) | 38.0 | 52.0 | 38.0 | 33.5 |
| Cyanide poisoning absent (n=21) | 26.0 | 30.0 | 24.0 | 44.0 |
| Cardiorespiratory arrest present (n=15) | 124.0 | 255.0 | 266.0 | 85.0 |
| Cardiorespiratory arrest absent (n=54) | 27.5 | 33.0 | 34.0 | 33.5 |
| **Alanine aminotransferase (ALT), IU/L** | | | | |
| All patients (n=69) | 31.5 | 26.5 | 26.0 | 29.0 |
| Cyanide poisoning present (n=42) | 33.0 | 28.0 | 26.0 | 26.0 |
| Cyanide poisoning absent (n=21) | 26.0 | 21.0 | 19.0 | 24.0 |
| Cardiorespiratory arrest present (n=15) | 112.0 | 114.5 | 101.0 | 67.0 |
| Cardiorespiratory arrest absent (n=54) | 23.0 | 24.5 | 21.0 | 26.0 |
| **Prothrombin, % activity** | | | | |
| All patients (n=69) | 87.0 | 75.5 | 79.0 | 83.0 |
| Cyanide poisoning present (n=42) | 83.0 | 69.0 | 72.0 | 83.0 |
| Cyanide poisoning absent (n=21) | 89.0 | 81.0 | 81.5 | 81.0 |
| Cardiorespiratory arrest present (n=15) | 65.5 | 58.0 | 35.5 | 65.0 |
| Cardiorespiratory arrest absent (n=54) | 91.0 | 80.5 | 83.0 | 83.0 |
| **Creatine phosphokinase, IU/L** | | | | |
| All patients (n=69) | 125.0 | 313.0 | 514.5 | 468.5 |
| Cyanide poisoning present (n=42) | 136.0 | 372.0 | 635.5 | 377.0 |
| Cyanide poisoning absent (n=21) | 114.0 | 300.0 | 433.0 | 940.5 |
| Cardiorespiratory arrest present (n=15) | 201.0 | 2820.0 | 2632.0 | 368.0 |
| Cardiorespiratory arrest absent (n=54) | 124.0 | 300.0 | 428.0 | 477.0 |
| **Differentiated blood cell count RBCs per mL $\times 10^6$** | | | | |
| All patients (n=69) | 4.1 | 3.8 | 3.9 | 3.7 |
| Cyanide poisoning present (n=42) | 4.2 | 3.7 | 3.8 | 3.5 |
| Cyanide poisoning absent (n=21) | 4.1 | 4.0 | 4.0 | 3.8 |
| Cardiorespiratory arrest present (n=15) | 4.1 | 3.7 | 3.7 | 3.7 |
| Cardiorespiratory arrest absent (n=54) | 4.2 | 4.0 | 4.0 | 3.7 |
| **Hemoglobin, g/L** | | | | |
| All patients (n=69) | 13.3 | 12.2 | 11.9 | 11.3 |
| Cyanide poisoning present (n=42) | 13.5 | 11.7 | 11.9 | 10.8 |
| Cyanide poisoning absent (n=21) | 13.2 | 12.6 | 12.6 | 11.5 |
| Cardiorespiratory arrest present (n=15) | 12.8 | 11.7 | 12.0 | 11.9 |
| Cardiorespiratory arrest absent (n=54) | 13.8 | 12.3 | 11.9 | 11.3 |
| **Hematocrit, %** | | | | |
| All patients (n=69) | 39.2 | 35.6 | 35.8 | 32.6 |
| Cyanide poisoning present (n=42) | 40.2 | 35.0 | 35.3 | 31.5 |
| Cyanide poisoning absent (n=21) | 39.2 | 36.3 | 37.1 | 33.1 |
| Cardiorespiratory arrest present (n=15) | 38.8 | 35.6 | 35.6 | 32.2 |

| | Day 0 | Day 1 | Day 2 | Day 3 |
|---|---|---|---|---|
| Cardiorespiratory arrest absent (n=54) | 40.0 | 35.6 | 35.9 | 32.6 |
| **Leukocytes per mL $\times 10^3$** | | | | |
| All patients (n=69) | 13.0 | 16.0 | 13.8 | 11.4 |
| Cyanide poisoning present (n=42) | 13.4 | 16.9 | 13.8 | 12.7 |
| Cyanide poisoning absent (n=21) | 13.3 | 16.0 | 15.6 | 11.4 |
| Cardiorespiratory arrest present (n=15) | 11.9 | 10.2 | 13.8 | 19.1 |
| Cardiorespiratory arrest absent (n=54) | 14.0 | 16.8 | 14.0 | 10.9 |
| **Platelets per mL $\times 10^3$** | | | | |
| All patients (n=69) | 261.0 | 217.5 | 191.0 | 217.5 |
| Cyanide poisoning present (n=42) | 281.0 | 214.0 | 235.0 | 257.0 |
| Cyanide poisoning absent (n=21) | 212.0 | 239.5 | 168.0 | 166.5 |
| Cardiorespiratory arrest present (n=15) | 230.0 | 214.0 | 122.0 | 243.0 |
| Cardiorespiratory arrest absent (n=54) | 272.0 | 221.0 | 206.0 | 196.0 |

*Laboratory reference ranges: Plasma lactate 0.5 to 2.2 mmol/L; creatinine 62 to 115 $\mu$mol/L for men and 53 to 97 $\mu$mol/L for women; blood glucose 3.33 to 5.55 mmol/L; total bilirubin 3 to 22 $\mu$mol/L; alkaline phosphatase 14 to 100 IU/L; aspartate aminotransferase 5 to 40 IU/L; alanine aminotransferase 7 to 56 IU/L, prothrombin 90% to 100% activity; creatine phosphokinase 60 to 320 IU/L for men and 50 to 200 IU/L for women; RBCs 4.2 to 6.9 per mL $\times 10^6$; hemoglobin 13 to 18 g/L for men and 12 to 16 g/L for women; hematocrit 42% to 52% for men and 37% to 47% for women; leukocytes 3.9 to 10.0 per mL $\times 10^3$; platelets 150 to 350 per mL $\times 10^3$.