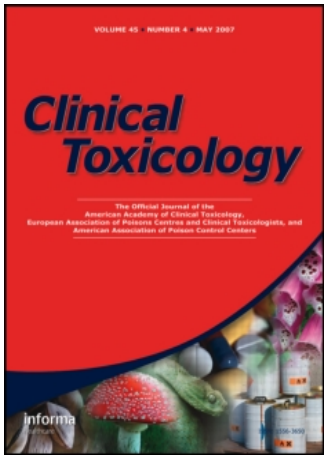

Clinical Toxicology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597279

Prehospital Administration of Hydroxocobalamin for Smoke Inhalation-Associated Cyanide Poisoning: 8 Years of Experience in the Paris Fire Brigade

Jean-Luc Fortin [a]; Jean-Pascal Giocanti [b]; Michel Ruttimann [c]; Jean-Jacques Kowalski [c]
[a] Emergency Department, Military Hospital Legouest, Metz, France
[b] Samu 25, Jean Minjoz Hospital, Besançon, France
[c] Emergency Medical Service, Paris Fire Brigade, Paris, France

Online Publication Date: 01 February 2006
To cite this Article: Fortin, Jean-Luc, Giocanti, Jean-Pascal, Ruttimann, Michel and Kowalski, Jean-Jacques (2006) 'Prehospital Administration of Hydroxocobalamin for Smoke Inhalation-Associated Cyanide Poisoning: 8 Years of Experience in the Paris Fire Brigade ', Clinical Toxicology, 44:1, 37 - 44
To link to this article: DOI: 10.1080/15563650600811870
URL: http://dx.doi.org/10.1080/15563650600811870

Clinical Toxicology, 44:37–44, 2006

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650600811870

informa
healthcare

ARTICLE

Prehospital Administration of Hydroxocobalamin for Smoke Inhalation-Associated Cyanide Poisoning: 8 Years of Experience in the Paris Fire Brigade

Jean-Luc Fortin, M.D.
Emergency Department, Military Hospital Legouest, Metz, France

Jean-Pascal Giocanti, M.D.
Samu 25, Jean Minjoz Hospital, Besançon, France

Michel Ruttimann, M.D., and Jean-Jacques Kowalski, M.D.
Emergency Medical Service, Paris Fire Brigade, Paris, France

Introduction. **This article reports the results of a retrospective study of 8 years of experience of the Paris Fire Brigade with the prehospital use of hydroxocobalamin.** ***Methods.*** **The head physician at the Paris Fire Brigade extracted and summarized data from standardized forms completed at the fire scene and, when available, hospital reports to assess survival status and clinical parameters associated with the use of hydroxocobalamin for each patient who received it for smoke inhalation-associated cyanide poisoning from 1995 to 2003.** ***Results.*** **Of the 101 patients administered hydroxocobalamin, 30 survived, 42 died (17 at the fire scene and 25 at the intensive-care unit), and survival status was not known in the remaining 29 patients. Among the 72 patients for whom survival status was known, survival rate was 41.7% after the administration of hydroxocobalamin. Of the 38 patients found in cardiac arrest, 21 had a return of spontaneous circulation during prehospital care. Of the 12 patients who were initially hemodynamically unstable (systolic blood pressure 0 to ≤90 mmHg), 9 recovered systolic blood pressure an average of 30.6 minutes after the start of hydroxocobalamin infusion. Among nonsedated patients in the sample as a whole (n = 52), mean (SD) Glasgow coma scale score improved from 7.9 (5.4) initially to 8.5 (5.7) after administration of hydroxocobalamin. Among nonsedated patients who were initially neurologically impaired (n = 18), Glasgow coma scale score improved in 9 patients, did not change in 8 patients, and worsened in 1 patient. Two adverse events—red or pink coloration of urine or skin (n = 5) and cutaneous rash (n = 1)—were assessed as being possibly related to hydroxocobalamin.** ***Conclusion.*** **Hydroxocobalamin has a risk:benefit ratio rendering it suitable for prehospital use in the management of acute cyanide poisoning caused by smoke inhalation.**

Keywords Cyanide; Hydroxocobalamin; Inhalation; Fire; Smoke; Antidote

INTRODUCTION

Inhalation of smoke in closed-space fires is an underrecognized but common source of cyanide poisoning (1,2), which plays a part in the approximately 4,000 fire-attributed deaths in the United States each year (2–4). Produced during combustion of nitrogen- or carbon-containing substances, hydrogen cyanide can be generated by the burning of synthetics such as polyurethane, acrylics, nylon, and plastics, as well as natural materials such as wool, silk, cotton, paper, and wood (5,6). Elevated cyanide levels are frequently found in victims of closed-space fires, and risk of smoke inhalation-associated death is directly related to the amount of cyanide exposure (2,7–14). Concurrent poisoning with carbon monoxide, a more widely recognized fire hazard, is common in victims of smoke inhalation-associated cyanide poisoning (15–17). These toxicants may be synergistically poisonous. In addition, cyanide can contribute to smoke inhalation-associated mortality independently of carbon monoxide as demonstrated by the finding of potentially lethal levels of blood cyanide in the absence of lethal carbon monoxide levels in victims who died of smoke inhalation (2,7,15).

As cyanide poisoning can culminate rapidly in death, successful intervention critically depends on minimizing the time between cyanide exposure and treatment (5). To be most effective, an antidote should be administered at the scene of the incident immediately after removal of the victim from the zone of

Some of the data described in this article were presented at the Fire Rescue International Congress, Las Vegas, Nevada, April 26–28, 2004, and at the European Burns Association meeting, Bergen, Norway, September 10–13, 2003.

Address correspondence to Dr. Jean-Luc Fortin, Emergency Department, Military Hospital Legouest, BP 10, 27 bd de Plantières, 57998, Metz Armées. E-mail: fortin.jeanluc@free.fr and fortin.jeanluc@wanadoo.fr

exposure. Intervention is most often undertaken on the basis of a presumptive diagnosis. Experts suggest that cyanide poisoning should be suspected in any person exposed to smoke in a closed-space fire regardless of whether burns have been sustained (2,17,18). Soot in the mouth or nose, altered consciousness, and presence of hypotension increase confidence in the diagnosis.

The only currently available cyanide antidote in the United States, the three-component Cyanide Antidote Kit containing sodium thiosulfate, amyl nitrite, and sodium nitrite, lacks a risk:benefit ratio conducive to such prehospital use in smoke-inhalation victims. The nitrite components of the kit reduce oxygenation of the blood by forming methemoglobin from hemoglobin. Antidote-induced methemoglobinemia can cause potentially fatal reduction in the oxygen-carrying capacity of the blood when superimposed on blood oxygen deficits associated with carboxyhemoglobinemia secondary to carbon monoxide poisoning (6,19,20). Other factors rendering the risk:benefit ratio of the Cyanide Antidote Kit poorly adapted to prehospital care include the potential for sodium nitrite to cause severe hypotension that can result in shock or death (20,21) and a relatively slow onset of action of sodium thiosulfate (22).

To address the need for an antidote with potential for prehospital use for cyanide poisoning from smoke inhalation and other causes, hydroxocobalamin, a precursor of vitamin B_{12}, is being studied for possible introduction in the United States. Hydroxocobalamin detoxifies cyanide by binding with it to form cyanocobalamin, which is excreted in urine, without compromising the oxygen-carrying capacity of the blood (5,23). Hydroxocobalamin has been used for decades in some European countries to treat acute cyanide poisoning and in 1996 received regulatory approval in France for this use. The European experience in the prehospital use of hydroxocobalamin for victims of smoke inhalation provides information relevant to assessing its potential utility in the United States prehospital setting. This article reports the results of an open-label, retrospective study of the Paris Fire Brigade's experience from 1995 to 2003 with the use of hydroxocobalamin for the treatment of suspected cyanide poisoning in smoke-inhalation victims.

METHODS

Study Design and Setting

The study was an open-label, retrospective review of case records of patients treated with hydroxocobalamin any time between 1995 and 2003 by members of the Paris Fire Brigade for suspected cyanide poisoning associated with smoke inhalation. The Paris Fire Brigade provides the first line of emergency medical services, including prehospital emergency care, to victims of fire and other emergencies in Paris and its environs, totaling a 759-km^2 area of 6,188,434 inhabitants (according to the 2002 census). The brigade consists of 77 fire centers staffed by 7,020 firemen and an emergency department staffed by 50 emergency-medicine physicians, 60 nurses, and 36 intensive-care ambulance drivers. Each of the 7 intensive-care mobile units is staffed at any given time by a doctor, nurse, and driver.

Patients

All smoke-inhalation victims who were treated in the prehospital setting during the study period with hydroxocobalamin for suspected cyanide poisoning were included in the study. No other inclusion or exclusion criteria were applied.

Treatment

Patients were treated with hydroxocobalamin (Cyanokit®; supplied in 250-mL vials containing 2.5 g lyophilized hydroxocobalamin for dilution with 100 mL sodium chloride 0.9%) and standard supportive care as soon as medically feasible at the scene of the fire. Hydroxocobalamin was administered by a trained nurse under direct supervision by an emergency physician of the Paris Fire Brigade, and in accordance with the summary of product characteristics and the Paris Fire Brigade Cyanokit Prehospital Treatment Guidelines. The guidelines specify that hydroxocobalamin be administered intravenously over 15 min at an initial dose of 5 g for adults and 70 mg/kg for children with the option to administer a second identical dose in the event of transient or incomplete response.

Data Extraction

The head physician at the Paris Fire Brigade (author Jean-Luc Fortin) retrospectively reviewed prehospital case records and, when available, hospital discharge summaries to determine survival status and clinical parameters associated with the use of hydroxocobalamin in all patients who received the antidote for smoke inhalation-associated cyanide poisoning during the 8-year period of 1995 to 2003. Data on the circumstances of smoke exposure; provision of prehospital care; hydroxocobalamin administration; carboxyhemoglobin concentration (measured in some patients upon arrival at the intensive care unit); patients' demographics; and pre-antidotal and post-antidotal clinical status, vital signs, and Glasgow coma scale scores (23) were extracted. The extent of burns was not recorded. In addition, prehospital and hospital reports were reviewed for reports of hydroxocobalamin-associated adverse events, defined as untoward medical occurrences arising during prehospital or hospital care. Blood cyanide concentrations were not measured.

Endpoints and Data Analysis

The main retrospectively defined efficacy measure was survival rate, which was summarized for the sample as a whole and for patients among whom survival status was known. Survival and other endpoints were assessed in the following subgroups, which were based on the predominant clinical sign at

initial evaluation: 1) patients in cardiac arrest; 2) patients in shock (systolic blood pressure <90 mmHg); 3) patients with neurological impairment (i.e., Glasgow coma scale score <15 or loss of consciousness); and 4) patients with smoke exposure but without clinical signs of cardiac arrest, shock, or neurological impairment.

Besides survival rate, additional efficacy measures included

- The proportion of patients initially found in cardiac arrest who recovered cardiac function at the fire scene after administration of hydroxocobalamin.
- Systolic blood pressure before, during, and after infusion of hydroxocobalamin for the subset of patients who were initially hemodynamically unstable (defined as having a systolic blood pressure >0 mmHg and ≤90 mmHg before administration of hydroxocobalamin).
- The proportion of hemodynamically unstable patients with hemodynamic improvement (i.e., recovery of systolic blood pressure to >90 mmHg) after administration of hydroxocobalamin.
- Changes in Glasgow coma scale score from initial evaluation to final evaluation at the fire scene among patients who did not receive sedating medications. The Glasgow coma scale score, which ranges from 3 to 15, reflects degree of neurologic impairment on the basis of ocular, verbal, and motor responses (24). Glasgow coma scale scores of ≥13 to <15, 9 to 12, and ≤8 reflect mild, moderate, and severe neurologic impairment, respectively.

The main retrospectively defined tolerability measure was adverse events, which were categorized *post hoc* as to causality and summarized. All data were summarized with descriptive statistics based on the total number of patients with available data for the relevant measure. No hypothesis testing was undertaken.

RESULTS

Study Sample

Between 1995 and 2003, the Paris Fire Brigade administered hydroxocobalamin for smoke inhalation-associated cyanide poisoning to 101 patients, of whom 38 were found in cardiac arrest, 5 were found in shock, and 46 were neurologically impaired (Table 1). Demographics of the sample as a whole and of these subgroups are shown in Table 1. In the sample as a whole, 52.5% of patients were male and mean (SD) age was 47.1 (20.7) years.

All patients were exposed to fire smoke resulting from a residential fire (Table 1). Additionally, 3 patients had attempted suicide with drugs, and 2 were victims of multiple trauma. Burns were present in approximately half of the sample (52.5%), and soot (predominantly in the mouth, nose, throat, and lower airways) was present in 71.3% of the sample (Table 1). Carbon monoxide poisoning (carboxyhemoglobin ≥10%) was found in 22 of the 36 patients who had carboxyhemoglobin measured upon arrival at the intensive care unit. Initial measurements at the fire scene for the sample as a whole show mean (SD) systolic blood pressure of 131.0 mmHg (34.1), diastolic blood pressure of 76.4 mmHg (15.7), pulse of 102.0 bpm (17.9), and Glasgow coma scale score of 8.0 (5.1) (Table 1).

Antidotal Treatment

The Paris Fire Brigade arrived at the fire scene a mean 8.6 minutes (SD = 3.6; range 2 to 18; n = 83) after the call to the firefighters. For the sample as a whole, the mean time between initiation of care and administration of hydroxocobalamin was 14.1 minutes. Hydroxocobalamin was administered at a median dose of 5.0 g (range 1 to 10) and a mean dose of 4.7 g (SD 1.4).

Survival

Of the 101 patients administered hydroxocobalamin, 30 survived, 42 died, and survival status was not known (because of lack of hospital summaries) in the remaining 29 (Table 2 and Fig. 1). When the 29 patients for whom survival status was unknown were excluded from the calculation, survival rate was 41.7% (30 of 72 patients) after administration of hydroxocobalamin (Table 2).

Of the 42 patients who died, 17 died at the fire scene, and 25 died at the intensive-care unit. Mean time to death was 4 days. Main cause of death was cardiac arrest (n = 18) followed by multiple organ failure (n = 10) and cerebral anoxia (n = 10). In the subgroup of patients found in cardiac arrest, the survival rate was lower and the mean time to death was shorter (1.9 days) than in the sample as a whole (Table 2).

Return of Spontaneous Circulation in Patients Found in Cardiac Arrest

Of the 38 patients found in cardiac arrest, 21 had a return of spontaneous circulation during prehospital care and were admitted to the intensive care unit. Most (19 of 21) of these patients died within 1 to 8 days of being admitted to the intensive care unit.

Assessments in Hemodynamically Unstable Patients

Twelve patients met the criterion for being hemodynamically unstable (defined as having a systolic blood pressure >0 mmHg and ≤90 mmHg) before administration of hydroxocobalamin. Hemodynamic improvement was observed in 9 of these 12 patients (75%) after administration of hydroxocobalamin. On average, systolic blood pressure was recovered 30.6 minutes (median 20, range 5 to 70) after the start of hydroxocobalamin administration.

TABLE 1
Demographics and initial clinical status of patients with suspected cyanide poisoning

	Sample (n = 101)	Found in cardiac arrest (n = 38)	Found in shock (n = 5)	Neurologically impaired (n = 46)	No predominant clinical sign (n = 12)
Male, n (%)	53 (52.5)	15 (39.5)	3 (60.0)	28 (60.9)	7 (58.3)
Age, years	n = 98	n = 37	n = 5	n = 44	n = 12
Mean (SD)	47.1 (20.7)	45.5 (23.8)	36.2 (13.3)	51.4 (19.5)	40.8 (13.3)
Median (range)	48.5 (2–88)	47.0 (2–87)	29.0 (23–55)	51.0 (11–88)	39.5 (24–68)
Burns present, n (%)					
Yes	53 (52.5)	15 (39.5)	4 (80.0)	27 (58.7)	7 (58.3)
No	23 (22.8)	4 (10.5)	0 (0)	17 (37.0)	2 (16.7)
Missing	25 (24.7)	19 (50.0)	1 (20.0)	2 (4.3)	3 (25.0)
Soot present, n (%)					
Yes	72 (71.3)	19 (50.0)	4 (80.0)	39 (84.8)	10 (83.3)
No	3 (3.0)	1 (2.6)	0 (0)	1 (2.2)	1 (8.3)
Missing	26 (25.7)	18 (47.4)	1 (20.0)	6 (13.0)	1 (8.3)
Localization of soot, n (%)	n = 72	n = 19	n = 4	n = 39	n = 10
No specified location	4 (5.6)	1 (5.3)	0 (0)	3 (7.7)	0 (0)
Superficial	4 (5.6)	1 (5.3)	1 (25.0)	2 (5.1)	0 (0)
Mouth, nose	18 (25.0)	5 (26.3)	2 (50.0)	7 (17.9)	4 (40.0)
Throat	30 (41.7)	7 (36.8)	0 (0)	18 (46.2)	5 (50.0)
Lower airways	16 (22.2)	5 (26.3)	1 (25.0)	9 (23.1)	1 (10.0)
Carboxyhemoglobin	n = 36	n = 8	n = 4	n = 21	n = 3
Mean (SD)	12.5 (8.1)	11.6 (8.7)	7.6 (4.1)	12.9 (7.6)	18.3 (13.5)
≥10%, n	22	3	2	13	2
<10%, n	14	5	2	8	1
Systolic blood pressure, mmHg	n = 61	NA	n = 5	n = 44	n = 12
Mean (SD)	131.0 (34.1)		86.6 (6.5)	134.3 (34.5)	137.1 (26.7)
Median (range)	128.0 (70–300)		88.0 (80–95)	129.0 (70–300)	132.5 (100–180)
Diastolic blood pressure, mmHg	n = 54	NA	n = 4	n = 38	n = 12
Mean (SD)	76.4 (15.7)		57.3 (4.9)	75.6 (14.6)	85.6 (15.4)
Median (range)	71.5 (50–118)		59.5 (50–60)	70.0 (50–118)	80.0 (67–110)
Pulse, bpm	n = 62	NA	n = 5	n = 45	n = 12
Mean (SD)	102.0 (17.9)		103.8 (27.5)	103.1 (17.8)	96.9 (14.0)
Median (range)	100.0 (64–140)		98.0 (76–135)	100.0 (67–140)	99.0 (64–120)
Glasgow coma scale score	n = 101	n = 38	n = 5	n = 46	n = 12
Mean (SD)	8.0 (5.1)	3.0 (0.0)	12.2 (3.8)	9.6 (4.1)	15.0 (0.0)
Median (range)	7.0 (3–15)	3.0 (3–3)	14.0 (6–15)	10.5 (3–15)	15.0 (15–15)

Glasgow Coma Scale Scores

Changes in Glasgow coma scale score could not be calculated for 49 patients because of administration of sedating drugs (n = 41) or missing data (n = 8). Among the 52 patients for whom changes in Glasgow coma scale score could be calculated, mean (SD) score increased from 7.9 (5.4) at initial evaluation to 8.5 (5.7) at final evaluation at the fire scene. Glasgow coma scale score improved in 10 patients, did not change in 41 patients, and worsened in 1 patient (Fig. 2). Among nonsedated patients who were neurologically impaired before treatment (n = 18), Glasgow coma scale score improved in 9 patients, did not change in 8 patients, and worsened in 1 patient (Fig. 3).

Adverse Events

Two adverse events—red or pink coloration of urine or skin and cutaneous rash—were reported as being possibly related to hydroxocobalamin. Red or pink coloration of urine or skin was reported in 5 patients. Cutaneous rash was reported upon admission to the intensive care unit in 1 patient. This patient, who had acquired immune deficiency syndrome (AIDS), was admitted to the intensive care unit with severe, extended burns and rhabdomyolysis. The patient died 19 days after admission from a deep coma associated with renal insufficiency. Adverse events considered not to be related to administration of hydroxocobalamin were cardiac arrest (n = 2), respiratory distress (n = 1), and

TABLE 2
Survival data

	Sample (n = 101)	Subgroup with known survival status (n = 72)	Found in cardiac arrest (n = 38)	Found in shock (n = 5)	Neurologically impaired (n = 46)	No predominant sign of cyanide poisoning (n = 12)
Survived, n (%)	30 (29.7)	30 (41.7)	2 (5.3)	3 (60.0)	20 (43.5)	5 (41.7)
Died, n (%)	42 (41.6)	42 (58.3)	34 (89.5)	1 (20.0)	6 (13.0)	1 (8.3)
At fire scene	17 (16.8)	17 (23.6)	17 (44.7)	0 (0)	0 (0)	0 (0)
At intensive care unit	25 (24.8)	25 (34.7)	17 (44.7)	1 (20.0)	6 (13.0)	1 (8.3)
Hospital data missing, n (%)	29 (28.7)	0 (0)	2 (5.3)	1 (20.0)	20 (43.5)	6 (50.0)
Time to death, days	n = 42	n = 42	n = 34	n = 1	n = 6	n = 1
Mean (SD)	4.0 (6.3)	4.0 (6.3)	1.9 (1.8)	3.0 (0)	14.8 (11.2)	9 (0)
Median (range)	1.0 (1–30)	1.0 (1–30)	1.0 (1–8)	3.0 (3–3)	17.0 (2–30)	9.0 (9–9)
Cause of death, n (%)	n = 42	n = 42	n = 34	n = 1	n = 6	n = 1
Cardiac arrest	18 (42.9)	18 (42.9)	18 (52.9)	–	–	–
Multiple organ failure	10 (23.8)	10 (23.8)	4 (11.8)	1 (100)	4 (66.7)	1 (100)
Cerebral anoxia	10 (23.8)	10 (23.8)	10 (29.4)	–	–	–
Other	4 (9.5)	4 (9.5)	2 (5.9)	–	2 (33.3)	–

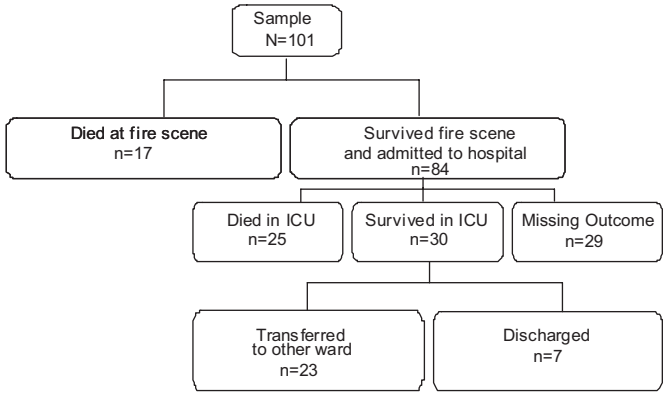

FIG. 1. Patient disposition. ICU = intensive care unit.

gastric hemorrhage in association with hepatic impairment and probable pre-existing cirrhosis (n = 1).

DISCUSSION

The United States currently lacks a cyanide antidote suitable for use in prehospital first-responder care. The unmet need is particularly acute for victims of smoke inhalation, which is often associated with carbon monoxide poisoning that precludes the safe use of the only available antidote in the United States. An antidote suitable for prehospital use is also needed to improve national readiness for, and response to, chemical terrorism involving cyanide (25). To address these concerns, the cyanide antidote hydroxocobalamin is being developed for possible introduction in the United States (25,26). The results of this retrospective review of 101 smoke-inhalation victims treated with hydroxocobalamin support the potential usefulness of the antidote in the prehospital setting. After administration of hydroxocobalamin, 30 patients survived, 42 died (17 at the fire scene and 25 at the intensive-care unit), and survival status was not known in the remaining 29 patients. Among the 72 patients for whom survival status was known, survival rate was 41.7% after administration of hydroxocobalamin. Of the 38 patients found in cardiac arrest, 21 had a return of spontaneous circulation at the fire scene after administration of hydroxocobalamin. Despite the return of spontaneous circulation at the fire scene in many of these patients, only 2 of the 38 patients found in cardiac arrest survived. This finding suggests that hydroxocobalamin might be most useful when administered before the onset of cardiac arrest.

Hydroxocobalamin administration was associated with stable systolic blood pressure in the sample as a whole and recovery of systolic blood pressure in 9 of the 12 patients who were hemodynamically unstable before antidote administration. These findings suggest that hydroxocobalamin might improve hemodynamic stability in smoke-inhalation victims. This attribute may be particularly important in the prehospital setting, where rapid attainment and maintenance of hemodynamic stability are crucial in saving lives and enabling timely transport to the hospital. The association of hydroxocobalamin administration with hemodynamic improvement in hypotensive patients is consistent with the previous finding of transient, self-limiting increases in systolic and diastolic blood pressure after administration of hydroxocobalamin 5 g to healthy volunteers who were heavy smokers (27) and the finding of modest elevations in blood pressure, which typically returned to baseline within 4 hours of infusion, in healthy volunteers administered hydroxocobalamin 2.5 to 10.0 g (28). The ability of hydroxocobalamin to scavenge the vasodilator nitric oxide might account for effects on hemodynamic parameters (29,30).

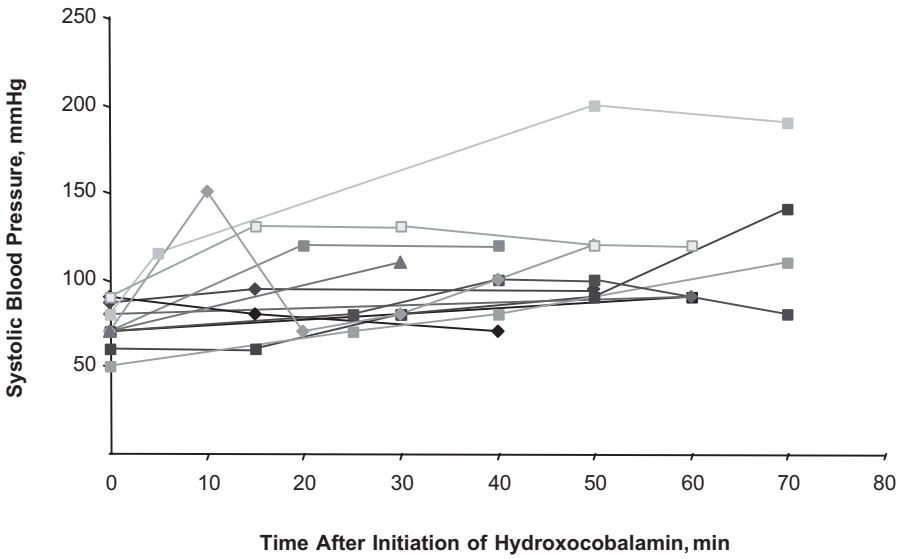

FIG. 2. Systolic blood pressure as a function of time after initiation of hydroxocobalamin infusion in 12 patients who were hemodynamically unstable before administration of hydroxocobalamin. Each line represents data from one patient.

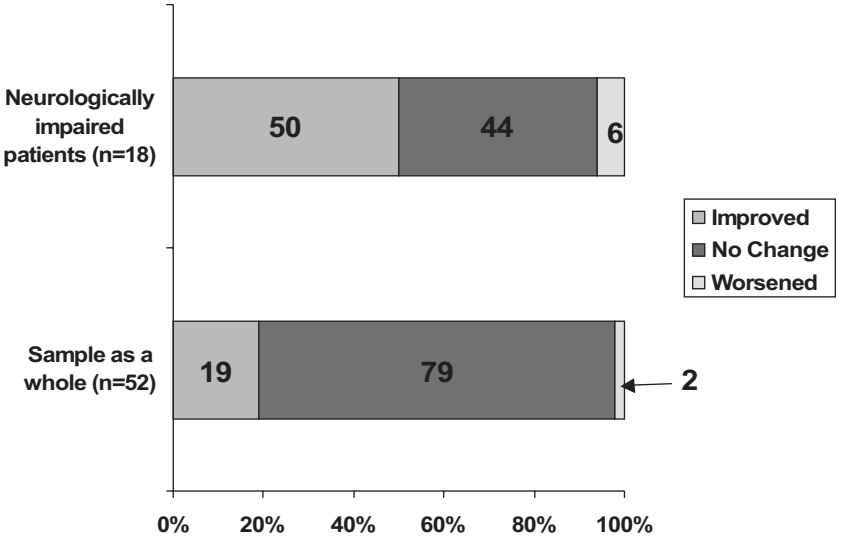

FIG. 3. Percentage of evaluable patients with improvement, no change, and worsening of Glasgow coma scale score in the sample as a whole (n = 52) and in the subgroup of patients who were neurologically impaired at baseline (n = 18).

The data on pre- and post-intervention neurologic impairment as measured by the Glasgow coma scale score are difficult to interpret given that the majority of patients were sedated or unconscious and, therefore, could not be evaluated for possible antidote-associated changes on this measure. In the 52 patients with evaluable data, Glasgow coma scale score improved slightly after hydroxocobalamin administration. Whether hydroxocobalamin can penetrate the blood-brain barrier to have antidotal action directly in the central nervous system is unknown (5). The effects of hydroxocobalamin on neurologic impairment associated with cyanide poisoning warrant additional study.

The Paris Fire Brigade did not systematically collect data on the safety and tolerability of hydroxocobalamin, but a review of patient records revealed no association of hydroxocobalamin with clinically significant untoward events. This result is consistent with previous studies, including prospective investigations of healthy volunteers and smoke-inhalation victims administered antidotal doses of hydroxocobalamin (23,26,28), in which no clinically significant adverse effects after acute

administration were reported. Because of the color of the molecule, hydroxocobalamin can cause a transitory, pink-to-red discoloration of the mucous membranes, skin, and urine—an adverse event observed in 5 patients in the current study. Additionally, hydroxocobalamin can interfere with colorimetric laboratory tests including aspartate aminotransferase, bilirubin, creatinine, and magnesium (32). Neither the skin and mucous membrane discoloration nor the interference with laboratory tests appears to reflect clinically meaningful changes, and they resolve within 2 to 3 days of hydroxocobalamin administration. Isolated allergic reactions have been reported after administration hydroxocobalamin (28,33,34).

The safety data available to date suggest that hydroxocobalamin can be administered without introducing significant risk of harm. This property renders hydroxocobalamin potentially suitable for use in the prehospital setting because it reduces the need to manage antidote-associated toxicities. The safety profile of hydroxocobalamin also may allow it to be used empirically with confidence in the prehospital or hospital setting for cases in which cyanide poisoning is suspected but not confirmed. The ability to administer an antidote for presumptive cyanide poisoning in the prehospital setting makes possible the rapid intervention crucial for successful treatment.

The data from this study should be interpreted in the context of its limitations. Humanistic and ethical considerations preclude undertaking placebo-controlled investigations that would provide information about the effectiveness of hydroxocobalamin compared with no antidotal intervention; therefore, the degree to which treatment with hydroxocobalamin is more effective than no intervention (or placebo) cannot be quantified. However, as severe cyanide poisoning of the nature observed in most patients in this study is nearly always fatal, the data support the conclusion that hydroxocobalamin is dramatically beneficial in patients with smoke inhalation-associated cyanide poisoning. The effectiveness of hydroxocobalamin in cases of poisoning caused by ingested cyanide also supports this conclusion (35–37). Besides lacking a control group, the study is also limited by the retrospective nature of the analysis and procedural and data-recording irregularities arising from the rigors of providing prehospital care to critically injured patients. Survival of victims of smoke inhalation is determined by many factors, including health status prior to smoke exposure and fire emergency-specific parameters such as amount and duration of smoke exposure, constituents of smoke, time between smoke exposure and intervention, and the extent of burns. This retrospective assessment included all comers regardless of their status with respect to these parameters. In that regard, this assessment differs from a clinical trial having entry criteria ensuring a uniform sample. The heterogeneous nature of the sample in the current study should be borne in mind in interpreting the data. Perhaps the most significant limitation of the study is the lack of available blood cyanide concentrations for this study sample. Because the severity of cyanide poisoning cannot be assessed on the basis of cyanide blood concentrations, it remains unclear whether some of the symptoms and severity was mainly due to other toxicants in the smoke.

These considerations notwithstanding, this study provides a valuable assessment of the effectiveness and safety of hydroxocobalamin as used in real-world prehospital care. The data suggest that hydroxocobalamin has a risk:benefit ratio that may be suitable for prehospital use in the management of acute cyanide poisoning caused by smoke inhalation.

ACKNOWLEDGMENT

The authors thanks Jane Saiers, Ph.D., for her assistance with writing this article. Dr. Saiers' work on this article was supported by EMD Pharmaceuticals, an affiliate of Merck KgaA and developer of hydroxocobalamin in the United States. Data analysis for this study was supported by EMD Pharmaceuticals.

REFERENCES

1. Walsh DW, Eckstein M. Hydrogen cyanide in fire smoke: an underappreciated threat. Emerg Med Serv 2004; 33:160–163.
2. Alarie Y. Toxicity of fire smoke. Crit Rev Toxicol 2002; 32:259–289.
3. American Academy of Pediatrics Committee on Injury and Poison Prevention. Reducing the number of deaths and injuries from residential fires. Pediatrics 2000; 105:1355–1357.
4. National Safety Council. Report on injuries in America 2001. July 28, 2003. (Accessed July 10, 2005, at http://www.nsc.org/library/rept2000. htm.)
5. Mégarbane B, Delahaye A, Goldgran-Tolédano D, et al. Antidotal treatment of cyanide poisoning. J Chin Med Assoc 2003; 66:193–203.
6. Jones J, McMullen MJ, Dougherty J. Toxic smoke inhalation: cyanide poisoning in fire victims. Am J Emerg Med 1987; 5:317–321.
7. Baud F, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. N Engl J Med 1991; 325:1761–1766.
8. Symington IS, Anderson RA, Thomson I, et al. Cyanide exposure in fires. Lancet 1978; 2(8080):91–92.
9. Anderson RA, Harland WA. Fire deaths in the Glasgow area: III. The role of hydrogen cyanide. Med Sci Law 1982; 22:35–40.
10. Wetherell HR. The occurrence of cyanide in the blood of fire victims. J Forensic Sci 1966; 11:167–173.
11. Pane GA, Mohler SR, Hamilton GC. The Cincinnati DC-9 experience: lessons in aircraft and airport safety. Aviat Space Environ Med 1985; 56:457–461.
12. Salomone J III, Sohn AP, Ritzlin R, Gauthier JH, McCarty V. Correlations of injury, toxicology, and cause of death to Galaxy Flight 203 crash site. J Forensic Sci 1987; 32:1403–1415.
13. Gill JR, Goldfeder LB, Stajic M. The Happy Land homicides: 87 deaths due to smoke inhalation. J Forensic Sci 2003; 48:161–163.
14. Levin BC, Rechani PR, Gurman JL, Landron F, Clark HM, Yoklavich MF, Rodriguez JR, Droz L, Mattos de Cabrera F, Kaye S. Analysis of carboxyhemoglobin and cyanide in blood from victims of the Dupont Plaza hotel fire in Puerto Rico. J Forensic Sci 1990; 35:151–168.
15. Silverman SH, Purdue GF, Hunt JL, Bost RO. Cyanide toxicity in burned patients. J Trauma 1988; 28:171–176.
16. Cohen MA, Guzzardi LJ. Inhalation of products of combustion. Ann Emerg Med 1983; 12:628–632.
17. Koschel MJ. Where there's smoke, there may be cyanide. Am J Nurs 2002; 102:39–42.
18. Augustine J. Smoke and fire: recognizing cyanide as a toxic agent. fireEMS 2005; May:18–23.
19. Becker CE. The role of cyanide in fires. Vet Hum Toxicol 1985; 27:487–490.

20. Hall AH, Kulig KW, Rumack BH. Suspected cyanide poisoning in smoke inhalation: complications of sodium nitrite therapy. J Toxicol Clin Exp 1989; 9:3–9.
21. Johnson WS, Hall AH, Rumack BH. Cyanide poisoning successfully treated without therapeutic methemoglobin levels. Am J Emerg Med 1989; 7:437–440.
22. Friedberg KD, Shukla UR. The efficiency of aquocobalamine as an antidote in cyanide poisoning when given alone or combined with sodium thiosulfate. Arch Toxicol 1975; 33:103–113.
23. Fortin JL, Ruttimann M, Domanski L, Kowalski JJ. Hydroxocobalamin: treatment for smoke inhalation-associated cyanide poisoning. Meeting the needs of fire victims. JEMS 2004; 29:(suppl):18–21.
24. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2:81–84.
25. Sauer SW, Keim ME. Hydroxocobalamin: improved public health readiness for cyanide disasters. Ann Emerg Med 2001; 37:635–641.
26. Hall AH, Walsh D, Maniscalco P. Hydroxocobalamin as a cyanide antidote in prehospital first responder care. JEMS 2004; 29(suppl):Abstract.
27. Forsyth JC, Mueller PD, Becker CE, Osterloh J, Benowitz N, Rumack BH, Hall AH. Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. Clin Toxicol 1993; 31:277–294.
28. Uhl W, Nolting A, Golor G, Rost KL, Kovar A. Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study. Clin Toxicol 2006; 44(S1):17–29.
29. Gerth K, Ehring T, Braendle M, Schelling P. Nitric oxide scavenging by hydroxocobalamin accounts for its hemodynamic profile. Clin Toxicol 2006; 44(S1):31–39.
30. Greenberg SS, Xie J, Zatarain JM, Kapusta DR, Miller MJ. Hydroxocobalamin (vitamin B12a) prevents and reverses endotoxin-induced hypotension and mortality in rodents: role of nitric oxide. J Pharmacol Exp Ther 1995; 273:257–265.
31. Houeto P, Borron SW, Sandouk P, Imbert M, Levillain P, Baud FJ. Pharmacokinetics of hydroxocobalamin in smoke inhalation victims. Clin Toxicol 1996; 34:397–404.
32. Curry SC, Connor DA, Raschke RA. Effect of the cyanide antidote hydroxocobalamin on commonly ordered serum chemistry studies. Ann Emerg Med 1994; 24:65–67.
33. Branco-Ferreira M, Clode MH, Pereira-Barbosa MA, Palma-Carlos AG. Anaphylactic reaction to hydroxycobalamin. Allergy 1997; 52:118–119.
34. Heyworth-Smith D, Hogan PG. Allergy to hydroxycobalamin, with tolerance of cyanocobalamin. Med J Aust 2002; 177:162–163.
35. Mannaioni G, Vannacci A, Marzocca C, Zorn AM, Peruzzi S, Morani F. Acute cyanide intoxication treated with a combination of hydroxycobalamin, sodium nitrite, and sodium thiosulfate. J Toxicol Clin Toxicol 2002; 40:181–183.
36. Hall AH, Rumack BH. Hydroxycobalamin/sodium thiosulfate as a cyanide antidote. J Emerg Med 1987; 5:115–121.
37. Borron S, Mégarbane B, Baud FJ. Hydroxocobalamin is an effective antidote in severe acute cyanide poisoning in man. Abstract. Int J Toxicol 2004; 23:399–400.