PREHOSPITAL HYDROXOCOBALAMIN FOR INHALATION INJURY AND CYANIDE TOXICITY IN THE UNITED STATES - ANALYSIS OF A DATABASE AND SURVEY OF EMS PROVIDERS

UTILISATION PRÉHOSPITALIÈRE D'HYDROXOCOBALAMINE POUR INHALATION DE FUMÉES ET INTOXICATION AU CYANURE AUX ÉTATS-UNIS. ANALYSE D'UNE BANQUE DE DONNÉES ET ÉVALUATION AUPRÈS DES SERVICES D'URGENCE

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SUMMARY. Prehospital use of hydroxocobalamin as an antidote for cyanide toxicity, a serious complication of smoke inhalation, has yet to be universally adopted in the United States though its efficacy and safety have been demonstrated since 2006. The purpose of this study was to characterize practices of prehospital hydroxocobalamin administration via a survey of emergency medical services (EMS) and to report a case series from an EMS database to track use of hydroxocobalamin. The Fire Smoke Coalition Newsletter emailed a voluntary survey to EMS subscribers regarding hydroxocobalamin use. Survey responses were analyzed in addition to survival data from the Smoke Inhalation Treatment Database (SITD), a publically available, self-reported, online database for EMS regarding smoke inhalation patient outcomes. Analysis was compared to current published data from PubMed. The survey had a 14% response rate (284/2000). Only 38% reported prehospital utilization of a hydrogen cyanide antidote with 46% using hydroxocobalamin. 20% of responders reported a formal ALS protocol was in place for hydroxocobalamin use. For the SITD, 12 of 13 (92%) patients who received hydroxocobalamin for suspected inhalation survived. Other studies found a survival rate of 72% and 42% after administration of hydroxocobalamin for smoke inhalation. Prehospital administration of hydroxocobalamin for cyanide toxicity is uncommon in the United States, as evidenced by this analysis, despite well-documented safety and efficacy. Although a small sample, patients who received prehospital hydroxocobalamin had improved survival. This survival rate is significantly greater than those reported previously.

Keywords: cyanide toxicity, hydroxocobalamin, inhalation injury, cyanokit®

RÉSUMÉ. *L'utilisation préhospitalière de l'hydroxocobalamine (OHB12) comme antidote du cyanure, intoxication grave compliquant les inhalations de fumées (IF), n'est toujours pas réalisée partout aux États-Unis, bien que son innocuité et son efficacité aient été démontrées dès 2006. Les buts de cette étude était de caractériser l'utilisation préhospitalière d'OHB12 à travers les données des services d'urgences (SU) et de rapporter une série de cas issus de leurs dossiers. La « Fire Smoke Coalition Newsletter » a proposé par courriel aux services d'urgence abonnés un étude sur l'utilisation d'OHB12, basée sur le volontariat. En plus des réponses, nous avons analysé les données de la « Smoke Inhalation Treatment Database » (STID), banque de données publique abondée par les SU, colligeant le devenir des patients victimes d'une IF et les avons comparées aux données de la littérature, retrouvée dans PubMed. Le taux de réponse au questionnaire a été de 14% (284/2 000). Trente huit pour cent des répondeurs utilisent des antidotes au cyanure en préhospitalier, qui est OHB12 dans 46% des cas. Vingt pour cent des répondeurs attestent de l'existence d'un protocole formalisé quant à l'utilisation d'OHB12. Selon STID, 92% (12/13) des patients ayant reçu OHB12 ont survécu. D'autres études retrouvent des taux de survie de 72% et 42% après administration de OHB12 dans le cadre de l'IF. Cette étude confirme que l'utilisation préhospitalière d'OHB12 dans le cadre de l'intoxication au cyanure n'est pas habituelle aux États-Unis, malgré une efficacité et une innocuité reconnues. Bien que l'échantillon soit faible, les patients ayant reçu OHB12 en préhospitalier ont un taux de survie nettement amélioré par rapport à ceux précédemment rapportés.*

Mots-clés: *intoxication au cyanure, inhalation de fumées, hydroxocobalamine, cyanokit®*

Introduction

In modern times, healthcare providers have become increasingly aware of the cyanide gas in fire smoke, which can lead to cyanide toxicity with smoke inhalation. As technology has advanced, buildings that were constructed of wood and

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brick are now constructed with synthetic building compounds. Furthermore, modern furniture is often comprised of synthetic compounds as well. When these plastics and synthetics ignite, cyanide gas is produced as a byproduct of combustion. The consequences of breathing cyanide gas are devastating to human cells. Cyanide poisoning impairs production of ATP and subsequent anaerobic metabolism, and in some cases, can be lethal.[1] Early symptoms of cyanide toxicity include agitation, headache, metallic taste, confusion, lethargy, diaphoresis, nausea, tachypnea, tachycardia and hypertension. Late symptoms of cyanide toxicity include vomiting, renal failure, hepatic necrosis, rhabdomyolysis, coma, convulsions, apnea, hypotension and bradyarrhythmias.[2] As cyanide poisoning remains an issue worldwide, the question of how and when to treat cyanide toxicity arises.

Hydroxocobalamin, also known as cyanokit®, is essentially a hydroxylated form of vitamin B_{12}. Hydroxocobalamin has been used in Europe since 1980 and was approved in 2006 by the FDA.[3] The mechanism of hydroxocobalamin involves rapidly removing cyanide from tissue by forming cyanocobalamin, which is then excreted unchanged in the urine.[4] It has been utilized by the Paris Fire Brigade in the prehospital setting, but there is very little data published on the subject.[5,6] Thus, the clinical efficacy of hydroxocobalamin in the management of prehospital fire-smoke inhalation injury and cyanide poisoning has been debated. In a retrospective review published in 2016, routine administration of hydroxocobalamin to smoke inhalation victims was found to be associated with decreased ventilator dependence times, decreased rates of pneumonia, and a reduction in time spent in the intensive care unit.[7] However, no clinical data is currently available to describe prehospital use of hydroxocobalamin in the United States.

Much confusion exists about the use of hydroxocobalamin, specifically with regard to its effectiveness and the timeline of administration. There is very little data on the prevalence of its availability, use and outcomes, especially in North American prehospital settings. The French studies aforementioned assisted in establishing a basis for hydroxocobalamin's efficacy for detoxifying cyanide poisoning.[5,6] However, very few Fire/EMS departments carry hydroxocobalamin.

The purpose of this study was to characterize practices of prehospital hydroxocobalamin administration via a survey of emergency medical service (EMS) first responders and to report a case series from a database employed by EMS to track use of hydroxocobalamin.

Materials and methods

The study was conducted in two parts. First, surveys were emailed to EMS subscribers of the Fire Smoke Coalition Newsletter. The survey aimed to determine if individual departments carried protocols regarding use of hydroxocobalamin or other cyanide treatments, and to determine the scope and circumstances of use. Second, the Smoke Inhalation Treatment Database (SITD) was analyzed to determine survival rates after hydroxocobalamin is administered in the field. This analysis was compared to current published data retrieved from PubMed regarding pre-hospital hydroxocobalamin administration for cyanide toxicity and inhalation injury in relation to mortality.

Survey data

A total of two thousand surveys were sent to EMS subscribers to the Fire Smoke Coalition newsletter. Questions focused on whether emergency responders carried hydroxocobalamin, if there were protocols for its administration to patients with suspected cyanide intoxication, and if responders have had success with its use. The survey questions also determined demographics of the respondent's department (volunteer, combination, or career) and level of service provided (Advanced Life Support (ALS) services or Basic Life Support (BLS) services). The final series of questions focused on use of hydroxocobalamin and other cyanide intoxication treatments. Participants were asked if they had perceived any "life-saving" results utilizing hydroxocobalamin for fire smoke exposure. Survey data was collected and analyzed.

Cyanide intoxication database analysis

The SITD, supported by the Fire Smoke Coalition, was then analyzed. The SITD is a publically available, self-reported, online database for first responders to submit data regarding smoke inhalation patient outcomes. This database was used to create a case series of patients who received hydroxocobalamin in the prehospital setting. Survival rates were determined. The data were then compared to the Paris Fire Brigade studies,[5,6] and trends and effects on mortality were determined.

Results

The survey was emailed to approximately two thousand subscribers and 284 responded (14%), whose demographics are detailed in *Table I*. 23% represented volunteer departments, 44% worked for career departments, and 33% were defined as mixed companies. More responders were BLS service providers. 112 of 277 (38%) respondents reported using a hydrogen cyanide antidote in the field (*Table II*). Of those 112 respondents, only 46% used hydroxocobalamin, and only 20% of the departments surveyed have a formal ALS treatment protocol in place for treating cyanide toxicity in smoke inhalation victims.

Table I - Fire Smoke Coalition survey data

Variable	Respondents	Percentage (%)
Respondents of the Fire Smoke Coalition's Newsletter	284/2000	14
Volunteer	66/284	23
Career	125/284	44
Combination Volunteer/Career	94/284	33
ALS Service	154/282	55
BLS Service	218/279	78

Table II - Analysis of prehospital practices survey

Variable	Respondents	Percentage (%)
SOP for monitoring cyanide during active firefighting	56/277	20
Department with prehospital use of cyanide antidote	112/277	38
Department with current prehospital use of hydroxocobalamin	51/112	46
ALS protocol involving use of cyanide antidote	60/280	21

Table III - Analysis of prehospital practices survival rate survey

Variable	Respondents	Percentage (%)
Survival rate of patients documented in Fire Smoke Coalition database[8]	12/13[8]	8
Prospective case study of Paris Fire Brigade total survival rate[6]	50/96[6]	72[6]
Retrospective review of Paris Fire Brigade total survival rate[5]	30/72[5]	42[5]

Analysis of the SITD revealed a survival rate of 92% (12/13) after administration of hydroxocobalamin in patients with smoke inhalation injury (*Table III*). Additionally, four respondents reported "life-saving" results after using hydroxocobalamin, described as an unresponsive patient who quickly became responsive after administration. This 92% survival rate with empiric prehospital use of hydroxocobalamin was much higher than the survival rates reported previously by Fortin et al.[5] and Borron et al.[6] of 72% and 42% respectively.

Discussion

Although hydroxocobalamin is the only FDA approved cyanide antidote, there is a paucity of data regarding its use.

The most recent prehospital studies of hydroxocobalamin were conducted by Fortin et al.[5] and Borron et al.[6] Fortin published a retrospective review which analyzed patients treated with hydroxocobalamin after inhalation injury. A 42% survival rate was determined. No serum cyanide levels were obtained.[5] Borron's study involved 69 patients treated by the Paris Fire Brigade who were monitored for clinical signs of cyanide toxicity while determining serum cyanide levels prior to administration of hydroxocobalamin. Borron's study established a 72% survival rate for patients treated with hydroxocobalamin.[6]

The only other clinical data available regarding hydroxocobalamin use after inhalation injury is derived from a retrospective study from Vanderbilt University. As described, this study demonstrated decreased ventilator dependence times, decreased rates of pneumonia, and a reduction in time spent in the intensive care unit after hydroxocobalamin administration.[7]

This prehospital case series demonstrated a much higher survival rate than the Paris studies,[5,6] keeping in mind the limitations of the data. The complete United States cohort was not captured in this analysis, as a self-reported database was utilized with a limited number of participants. This method is inherently susceptible to multiple forms of bias. Currently, the medical community has no understanding of how often hydroxocobalamin is utilized in the United States.

The results call attention to a paucity of data but do not provide high-quality evidence needed to determine the clinical efficacy of the treatment. However, given the fact that this therapy might greatly improve morbidity and mortality associated with smoke inhalation and the antidote has virtually no toxicity, there seems to be little downside to its use other than cost. Users must also understand that hydroxocobalamin turns the skin and urine of patients a reddish-purple color. Potentially, this could interfere with the timely recognition of rhabdomyolosis and with burn depth assessment.

Although analysis of the Smoke Inhalation Treatment Database is lacking in clinical detail and outcomes data, it raises an important issue - perception of the first responder. Understanding perceptions of the providers who will be administering hydroxocobalamin product is significant when considering whether it has the potential to become universally adopted or considered standard of care. Hydroxocobalamin appears to be a very promising therapy but needs further investigation in larger, multicenter studies.

Conclusions

Prehospital administration of hydroxocobalamin for cyanide toxicity is uncommon in the United States, as evidenced by this analysis, despite well-documented safety and efficacy. Although a small sample, the patients who received hydroxocobalamin in the prehospital setting had improved survival. This survival rate in the current study is significantly greater than those reported by previous publications. Larger, multicenter studies are needed to definitively establish standard of care.

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