Clinical Toxicology, 44:1–3, 2006
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ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650600811607

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EDITORIAL

Hydroxocobalamin for Acute Cyanide Poisoning: New Data from Preclinical and Clinical Studies; New Results from the Prehospital Emergency Setting

The World Health Organization (WHO) considers cyanide to be a priority chemical with respect to the environment and human health (1). Acute exposure to cyanide causes significant morbidity and mortality in structural fires, household and industrial accidents, suicides, attempted genocides, and wars (2,3). In western countries, including the United States, smoke inhalation is the most common source of poisoning with cyanide, which appears to be at least as important as carbon monoxide as a toxicant in fire smoke (4,5). In studies that measure it, cyanide is found in the blood of most victims of structural fires (5). Acute cyanide poisoning from fire smoke also poses a significant risk to fire professionals, as illustrated by the recent confirmation of acute cyanide poisoning in five firefighters who fought a fire at a Providence, Rhode Island, restaurant in March 2006. Cyanide is also a potential terrorist weapon (6). Several instances of planned use of cyanide in terrorism have been exposed in the past 3 years in the United States alone (6).

Awareness of cyanide risk has increased with growing recognition of the role of cyanide in smoke-inhalation morbidity and mortality and its potential for use as a terrorist weapon. In the United States, preparedness for managing individual and multiple-victim exposures to cyanide has not kept pace with increasing awareness of cyanide risk. Success in the treatment of cyanide poisoning is time-critical: antidote administration soon after exposure can prevent death, but delayed administration allows increased morbidity and mortality. Furthermore, because no laboratory test can confirm the presence of acute cyanide poisoning quickly, acute cyanide poisoning must be treated empirically on the basis of a presumptive diagnosis.

Of several cyanide antidotes available around the world, only one, the Cyanide Antidote Kit, is approved for use in the United States. In some areas, paramedic personnel are authorized to use the Cyanide Antidote Kit. A three-component kit consisting of amyl nitrite, sodium nitrite, and sodium thiosulfate, the Cyanide Antidote Kit does not have an optimal risk:benefit ratio. Its use requires rapid dosage calculations (always dangerous under urgent conditions), and its components have potentially serious toxicity. Nitrites cause potent vasodilation, leading to hypotension and potentially compounding pre-existing shock associated with cyanide poisoning (7). In addition, nitrite-induced methemoglobinemia reduces the oxygen-carrying capacity of the blood—a potentially harmful effect in critically ill patients with pre-existing compromise of blood oxygenation (8,9). The potential adverse interaction of methemoglobinemia and carboxyhemoglobinemia creates a therapeutic dilemma regarding the early use of the Cyanide Antidote Kit: is it best to treat presumed cyanide toxicity early, or will early treatment worsen the condition of patients who are likely to have concurrent carbon monoxide poisoning? Although sodium thiosulfate is sometimes given without the nitrite components of the kit in order to circumvent these risks, this option is suboptimal because of the relatively slow onset of action of sodium thiosulfate (10). Because of the limitations of the Cyanide Antidote Kit, many governmental agencies have deprioritized or omitted the role of antidotal treatment in the management of cyanide exposure in weapons-of-mass-destruction (WMD) planning. The kit is complicated to administer, causes adverse events, and has a short shelf life, necessitating frequent replacement.

A safe and effective antidote that is suitable for the treatment of known or suspected cyanide poisoning in the prehospital setting is needed (11). Hydroxocobalamin, a cyanide antidote licensed in France in 1996, may fulfill these characteristics (11). Hydroxocobalamin detoxifies cyanide by forming cyanocobalamin, which is excreted in urine, without compromising the oxygen-carrying capacity of the blood or causing hypotension (12,13). In an attempt to address the need for a cyanide antidote with a risk:benefit ratio favorable for prehospital use, hydroxocobalamin is being investigated for potential introduction in the United States. This supplement describes results of several studies conducted to support potential US licensing of hydroxocobalamin. The papers provide new data from preclinical and clinical studies as well as results from the prehospital emergency setting.

Successful prehospital and hospital use of hydroxocobalamin for cyanide poisoning from smoke inhalation, ingestion, and occupational exposure has been documented in case reports and series and in a prospective study of fire victims (13–17), but the efficacy of hydroxocobalamin for cyanide poisoning has not been evaluated in a placebo-controlled clinical trial. In conditions that are difficult to study in humans, animal data provide an important initial assessment of the potential usefulness of a treatment. In *Efficacy of Hydroxocobalamin for the Treatment of Acute Cyanide Poisoning in Adult Beagle Dogs*, Borron and colleagues

assess the efficacy of hydroxocobalamin in a randomized, blinded trial of acute cyanide poisoning in adult beagle dogs. Hydroxocobalamin reduced mortality compared with saline vehicle and was not associated with untoward effects when administered to dogs in the same formulation, via the same administration route, and at doses producing comparable exposure as those in humans.

Hydroxocobalamin is frequently used in France for the treatment of smoke-inhalation victims with presumed cyanide toxicity. The most common side effects of hydroxocobalamin in humans are reddish discoloration of the mucous membranes, skin, and urine and interference with specific colorimetric clinical laboratory values (12–15,18,19). These effects, which are attributed to the red color of the hydroxocobalamin molecule, are not thought to be clinically important; however, their potential clinical significance has not been systematically assessed. To further assess hydroxocobalamin safety, Uhl and colleagues conducted a placebo-controlled study in healthy volunteers—*Safety of Hydroxocobalamin in Healthy Volunteers in a Randomized, Placebo-Controlled Study*. The results are consistent with previous studies and French postmarketing experience in cyanide-exposed patients in suggesting that the safety profile of hydroxocobalamin supports empiric prehospital or hospital use.

Unlike the Cyanide Antidote Kit, which can produce hypotension, hydroxocobalamin has been associated with modest increases in blood pressure in animals and humans (14–16,20–22). Acute hemodynamic recovery, characterized by an increase in blood pressure, was documented in several studies after hydroxocobalamin was given for cyanide poisoning to patients found hypotensive or in cardiorespiratory arrest (14–16). Schelling and colleagues further characterize the effects of hydroxocobalamin on blood pressure and its potential mechanisms in *Nitric Oxide Scavenging by Hydroxocobalamin May Account for Its Hemodynamic Profile*. In corroboration of previous research, a modest increase in blood pressure was observed after administration of antidotal doses of hydroxocobalamin to anesthetized rabbits. Administration of L-N^{ω}-nitro-L-arginine methyl ester (L-NAME) to deplete nitric oxide abolished the effect of hydroxocobalamin on blood pressure, a finding suggesting that nitric oxide binding by hydroxocobalamin is involved in this effect.

Treatment of smoke inhalation-associated cyanide poisoning is a key potential application of hydroxocobalamin in the United States. In Paris, investigators have used and studied the effectiveness of hydroxocobalamin for more than 20 years. Their experience is unparalleled and has major importance in the potential use of hydroxocobalamin in the United States. In their manuscript *Prehospital Administration of Hydroxocobalamin for Smoke Inhalation-Associated Cyanide Poisoning: 8 Years of Experience in the Paris Fire Brigade*, Fortin and colleagues describe the results of a retrospective study assessing the safety and efficacy of hydroxocobalamin in smoke-inhalation victims with suspected cyanide poisoning. The results suggest that hydroxocobalamin has a risk:benefit ratio rendering it suitable for use in prehospital settings and intensive care units in the management of acute cyanide poisoning caused by smoke inhalation.

Together, the studies in this supplement—which includes the first vehicle-controlled evaluation of hydroxocobalamin efficacy in an animal model of acute cyanide poisoning and the first placebo-controlled assessment of hydroxocobalamin safety in humans—constitute an important addition to the growing body of knowledge about the profile of hydroxocobalamin as a cyanide antidote. These data suggest that hydroxocobalamin offers the potential for improving outcomes for victims of cyanide poisoning in the United States.

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