Sodium Nitrite and Sodium Thiosulfate Are Effective Against Acute Cyanide Poisoning When Administered by Intramuscular Injection

Vikhyat S. Bebarta, MD; Matthew Brittain, PhD; Adriano Chan, BS; Norma Garrett, PhD; David Yoon, MS; Tanya Burney, BS; David Mukai, BS; Michael Babin, DVM; Renate B. Pilz, MD; Sari B. Mahon, PhD; Matthew Brenner, MD; Gerry R. Boss, MD*

*Corresponding Author. E-mail: gboss@ucsd.edu.

Study objective: The 2 antidotes for acute cyanide poisoning in the United States must be administered by intravenous injection. In the out-of-hospital setting, intravenous injection is not practical, particularly for mass casualties, and intramuscular injection would be preferred. The purpose of this study is to determine whether sodium nitrite and sodium thiosulfate are effective cyanide antidotes when administered by intramuscular injection.

Methods: We used a randomized, nonblinded, parallel-group study design in 3 mammalian models: cyanide gas inhalation in mice, with treatment postexposure; intravenous sodium cyanide infusion in rabbits, with severe hypotension as the trigger for treatment; and intravenous potassium cyanide infusion in pigs, with apnea as the trigger for treatment. The drugs were administered by intramuscular injection, and all 3 models were lethal in the absence of therapy.

Results: We found that sodium nitrite and sodium thiosulfate individually rescued 100% of the mice, and that the combination of the 2 drugs rescued 73% of the rabbits and 80% of the pigs. In all 3 species, survival in treated animals was significantly better than in control animals (log rank test, $P<.05$). In the pigs, the drugs attenuated an increase in the plasma lactate concentration within 5 minutes postantidote injection (difference: plasma lactate, saline solution–treated versus nitrite- or thiosulfate-treated 1.76 [95% confidence interval 1.25 to 2.27]).

Conclusion: We conclude that sodium nitrite and sodium thiosulfate administered by intramuscular injection are effective against severe cyanide poisoning in 3 clinically relevant animal models of out-of-hospital emergency care. [Ann Emerg Med. 2017;69:718-725.]

Please see page 719 for the Editor's Capsule Summary of this article.

Readers: click on the link to go directly to a survey in which you can provide **feedback** to *Annals* on this particular article.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2016.09.034

INTRODUCTION

Background and Importance

Cyanide is a highly toxic chemical used in a wide variety of industries and is generated in industrial and residential fires.[1-3] It can be made relatively easily, and terrorists could poison food or medicines or detonate a cyanide bomb in an enclosed space.[4,5] Thus, cyanide exposure can occur under a variety of situations, and mass casualties are possible. Available treatments for cyanide poisoning such as hydroxocobalamin (Cyanokit) and the combination of sodium nitrite and sodium thiosulfate (Nithiodote) are administered by intravenous injection, which is not practical for treating a large number of cyanide-poisoned victims in the out-of-hospital setting. In a mass casualty scenario, probably the best treatment mode for critically ill patients would be intramuscular injection of antidote by first responders, preferably from a prefilled autoinjector. This requires that the antidote be stable in solution, sufficiently soluble to be administered in 1- to 3-mL doses, highly potent such that only a relatively small amount needs to be administered, and rapidly absorbed after intramuscular injection. Sodium nitrite and sodium thiosulfate are very soluble in water and stable under anaerobic conditions. Nithiodote contains 12.5 g of sodium thiosulfate, an amount far greater than could be administered by intramuscular injection, and published data indicate that neither sodium nitrite nor sodium thiosulfate is effective by intramuscular injection.[6,7] However, as part of our work of developing the cobalamin analog cobinamide as a cyanide antidote, we found recently that sodium nitrite and sodium thiosulfate showed some anticyanide activity when administered by intramuscular injection.[8-10]

Editor's Capsule Summary

What is already known on this topic

Cyanide poisoning requires rapid antidote administration, although the current antidotes require intravenous access.

What question this study addressed

Can cyanide antidotes sodium nitrite and sodium thiosulfate be effective if administered intramuscularly?

What this study adds to our knowledge

Using 3 distinct nonblinded animal models with objective endpoints, postexposure treatment with intramuscular cyanide antidote after lethal cyanide poisoning was highly effective at improving surrogate markers and preventing death.

How this is relevant to clinical practice

This animal model does not directly translate into human use, but suggests that additional study is warranted, particularly in the mass casualty setting.

Goals of This Investigation

Our goal was to rigorously assess whether sodium nitrite and sodium thiosulfate are effective when administered by intramuscular injection by testing them in 3 well-established lethal mammalian models of cyanide poisoning: a mouse model of inhalational cyanide exposure that simulates a scenario of gaseous cyanide poisoning,[8,10,11] a rabbit model in which severe hypotension is the trigger for treatment,[9,12,13] and a pig model in which apnea is the trigger for treatment.[14-16]

MATERIALS AND METHODS

Study Design

According to general HAZMAT principles, persons exposed to toxic chemicals should be evacuated immediately from the contaminated area, but it would be difficult to remove a large number of victims quickly from a confined, hard-to-access location such as a subway station. In these cases, it would be useful to treat the victims as quickly as possible before or during evacuation from the contaminated area. In consideration of these worst-case scenarios, our 3 animal models incorporate continued exposure to cyanide, even after treatment. This makes the models extremely rigorous because the antidote has to neutralize not just the amount of cyanide that triggered treatment—cardiovascular and respiratory collapse in the rabbits and pigs, respectively—but also cyanide that continued to be administered to a profoundly ill animal (Figure E1, available online at http://www.annemergmed.com). We studied 3 different species because we wanted to ensure that our findings were not limited to 1 or 2 species; because efficacy testing cannot be performed in human beings for a cyanide antidote, greater assurance is important in preclinical studies compared with that for most drug development programs.

The investigation was conducted as a randomized, nonblinded, parallel-group study. Animals were randomized to the control or treated group with a block randomization procedure to ensure equal numbers of animals in each group. Sample size was determined by a χ^2 test, with α=.05 and power=0.9 for the mice and rabbits and 0.8 for the pigs (the pigs were 50 kg, and we wanted to use a minimum of animals). From pilot studies and previous work, we expected 100% lethality in untreated mice and pigs, and 80% lethality in untreated rabbits.[8-16] Assuming 90% survival in treated animals, sample sizes were calculated for the mice, rabbits, and pigs as 6, 11, and 5, respectively.

The following sections provide a general description of the 3 animal models; full experimental details are in Appendix E1, available online at http://www.annemergmed.com.

Mice are small enough that they can be exposed to cyanide gas within a sealed chamber; this minimizes the risk of exposing laboratory personnel to cyanide, but it allows only visual monitoring of the animals. The mice were exposed to 587 ppm hydrogen cyanide (HCN) gas for 15 minutes, injected with test antidote, and then reexposed to the gas for 25 minutes (Figure E1*A*, available online at http://www.annemergmed.com). This model assumes that approximately 15 minutes are required for emergency medical personnel to arrive at a disaster scene and another 25 minutes are required to treat and evacuate the victims. As required by our Institutional Animal Care and Use Committee (IACUC), the mice were anesthetized by injection of isoflurane into the chamber to a final concentration of 2%; at 30°C (86°F), the isoflurane rapidly vaporizes and anesthetizes the mice. We used 8- to 12-week-old male C57BL/6J mice, purchased from Jackson Laboratories (Bar Harbor, ME), and injected them in the right gastrocnemius muscle with either 50 μL saline solution (control group) or 50 μL of the indicated concentrations of sodium nitrite or sodium thiosulfate.

The heart and central respiratory center are major cyanide targets, and we wanted to determine whether sodium nitrite and sodium thiosulfate could rescue animals from both cardiovascular and respiratory collapse.[1,17] Because it would be technically difficult to have a single