Hydroxocobalamin Versus Sodium Thiosulfate for the Treatment of Acute Cyanide Toxicity in a Swine (*Sus scrofa*) Model

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Study objective: We compare the efficacy of hydroxocobalamin to sodium thiosulfate to reverse the depressive effects on mean arterial pressure in a swine model of acute cyanide toxicity and gain a better understanding of the mechanism of action of the hydroxocobalamin in reversal of the toxicity.

Methods: Swine were intubated, anesthetized, and instrumented with central arterial and venous lines and a pulmonary artery catheter. Animals (n=36) were randomly assigned to one of 3 groups: hydroxocobalamin alone (150 mg/kg), sodium thiosulfate alone (413 mg/kg), or hydroxocobalamin (150 mg/kg)+sodium thiosulfate (413 mg/kg) and monitored for 60 minutes after the start of antidotal infusion. Cyanide was infused until severe hypotension developed, defined as blood pressure 50% of baseline mean arterial pressure. Repeated-measures ANOVA was used to determine statistically significant changes between groups over time.

Results: Time to hypotension (25, 28, and 33 minutes), cyanide dose at hypotension (4.7, 5.0, and 5.6 mg/kg), and mean cyanide blood levels (3.2, 3.7, and 3.8 μg/mL) and lactate levels (7, 8.2, 8.3 and mmol/L) were similar. All 12 animals in the sodium thiosulfate group died compared with 2 of 12 in the hydroxocobalamin/sodium thiosulfate group and 1 of 12 in hydroxocobalamin group. No statistically significant differences were detected between the hydroxocobalamin and hydroxocobalamin/sodium thiosulfate groups for carbon monoxide, mean arterial pressure, cyanide levels, or mortality at 60 minutes. Lactate level (2.6 versus 2.1 mmol/L), pH (7.44 versus 7.42), and bicarbonate level (25 versus 26 mEq/L) at 60 minutes were also similar between groups.

Conclusion: Sodium thiosulfate failed to reverse cyanide-induced shock in our swine model of severe cyanide toxicity. Further, sodium thiosulfate was not found to be effective when added to hydroxocobalamin in the treatment of cyanide-induced shock. Hydroxocobalamin alone was again found to be effective for severe cyanide toxicity. [Ann Emerg Med. 2012;59:532-539.]

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INTRODUCTION

Background

Cyanide toxicity can induce rapid deleterious effects of tachycardia, profound hypotension, and cardiac arrest. Shock and cardiac arrest are common and can occur in 50% of cyanide-exposed patients.[1]

Sodium nitrite combined with sodium thiosulfate has been the traditional antidotal treatment for cyanide poisoning and has been marketed as the Cyanide Antidote Kit.[2] Because of the sodium nitrite's adverse effects of hypotension and methemoglobinemia, use of sodium thiosulfate alone has been supported.[3-6] However, animal studies demonstrating its efficacy as a single antidote are conflicting and no human trial has been reported, to our knowledge.[7-10] Human case reports have been published, but in most cases sodium thiosulfate was used with another antidote.

Hydroxocobalamin was approved by the Food and Drug Administration for treatment of cyanide toxicity after efficacy was documented from animal studies and case series in Europe.[1] We have previously reported that hydroxocobalamin with sodium thiosulfate is as efficacious as sodium nitrite and sodium thiosulfate in an animal model of acute severe cyanide toxicity.[11] In addition, we found that hydroxocobalamin

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Editor's Capsule Summary

What is already known on this topic

Hydroxocobalamin is approved for treatment of cyanide toxicity. No published report has directly compared hydroxocobalamin and sodium thiosulfate or their combination.

What question this study addressed

In a clinically relevant randomized, blinded swine model of cyanide toxicity, 12 pigs were treated with hydroxocobalamin, 12 with sodium thiosulfate, and 12 with both.

What this study adds to our knowledge

Hydroxocobalamin alone reversed shock caused by cyanide poisoning. Sodium thiosulfate alone failed to reverse cyanide-induced shock and also failed to improve any tested measure of cyanide toxicity when added to hydroxocobalamin.

How this is relevant to clinical practice

Sodium thiosulfate is not useful in the treatment of acute cyanide cardiovascular toxicity in swine. Confirmation in humans would be helpful.

improved blood pressure, lactate levels, and cyanide levels more than sodium nitrite. However, it is not clear whether the sodium thiosulfate adds a beneficial effect to hydroxocobalamin alone.[3,6,11,12] Experts have recommended a trial comparing hydroxocobalamin alone with hydroxocobalamin with sodium thiosulfate.[4,5,12]

To our knowledge, no published report has directly compared hydroxocobalamin with sodium thiosulfate in a hypotensive, clinically relevant animal model.[13-16] Older studies had indirect outcomes or used small, simple models.[15,17] Recent studies compared hydroxocobalamin with control and used respiratory depression, a mild symptom of cyanide toxicity.[14] Most critically ill cyanide toxic patients are hypotensive.[18] In addition, to our knowledge no published, clinically relevant reports have compared hydroxocobalamin to hydroxocobalamin with sodium thiosulfate to evaluate the theoretic adjunctive benefit of sodium thiosulfate.

Goal of This Investigation

The primary hypothesis of our study is that sodium thiosulfate is as effective as hydroxocobalamin in reversing the hypotension associated with acute cyanide toxicity in our swine model. We also hypothesized that the addition of sodium thiosulfate would improve the efficacy of the hydroxocobalamin in our model.

MATERIALS AND METHODS

Study Design and Setting

We conducted a randomized comparative laboratory investigation. The study was approved by our Institutional Animal Care and Use Committee. All procedures involving animals complied with the regulations and guidelines of the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the American Association for Accreditation of Laboratory Animal Care. The housing of animals and the performance of the study took place in the Animal Care Facility at our institution.

Yorkshire swine (*Sus scrofa*) (N=36, weighing 48 to 52 kg) of both sexes were premedicated with intramuscular ketamine 10 mg/kg. General anesthesia was induced with isoflurane by nose cone. After tracheal intubation, the animals were mechanically ventilated with a volume-limited, time-cycled ventilator (Fabius GS anesthesia machine; Drager-Siemens, New York, NY) and maintained with inhaled isoflurane (1% to 3%) and oxygen (FiO_2 of 0.4 to 0.45). The tidal volume was initially 8 to 10 mL/kg, and the respiratory rate was 12 breaths/min. The minute ventilation was adjusted to maintain an end tidal CO_2 value between 38 and 42 mm Hg, as measured by inline capnography. Lead II of the surface ECG was monitored continuously. Temperature was maintained at 37.5°C (99.5°F) to 39°C (102°F). Baseline biochemical variables (arterial blood gas, hematocrit, methemoglobin, and electrolyte levels) were measured.

Interventions

Invasive hemodynamic variables were measured with an 8-French Swan-Ganz CCOmbo pulmonary artery catheter (model 746HF8) and the Edwards Vigilance II monitor (Edwards Lifesciences, Irvine, CA). Measurements included continuous cardiac output, systemic vascular resistance, mixed venous oxygen saturation, central venous pressure, pulmonary artery pressure, and core temperature. The catheter ports were flushed with saline solution and the catheter was placed by cutdown in the right external jugular. Aortic pressure was measured continuously through the femoral artery. An 8.5-French introducer (Arrow, Reading, PA) was placed in the carotid artery for laboratory sampling and another was placed in the femoral vein for medication administration. The animals received a warmed saline solution intravenous bolus (15 mL/kg) during procedure setup. Heparin (100 U/kg) was administered intravenously after catheters were inserted. The Fabius GS anesthesia data collection software embedded in the ventilator's computer was used for data acquisition at 1-minute intervals.

Baseline biochemical measurements included oxygen saturation, $PaCO_2$, PaO_2, and pH (ABL 800 Flex blood gas analyzer; Radiometer America, Westlake, OH), methemoglobin and hemoglobin (OSM3 Hemoximeter; Radiometer), and electrolytes (Piccolo Chemistry Analyzer; Abaxis, Union City, CA). We could not measure nitric oxide directly because the orange color of hydroxocobalamin interfered with the colorimetric chemiluminescent analyzer (Sievers Nitric Oxide

Table 1. Baseline characteristics of the animals.*

Characteristics	Hydroxocobalamin (N=12)	Hydroxocobalamin+Sodium Thiosulfate (N=12)	Sodium Thiosulfate (N=12)
Weight, kg	49 (2)	51 (2)	49 (2)
Pulse rate, beats/min	92 (14)	81 (6)	87 (13)
Systolic blood pressure, mm Hg	107 (13)	122 (11)	104 (7)
Mean arterial pressure, mm Hg	84 (10)	94 (9)	80 (3)
Cardiac output, L/min	5.0 (0.8)	5.1 (0.8)	4.8 (0.9)
Systemic vascular resistance, dynes-sec/cm^5	1,366 (234)	1,511 (282)	1,448 (340)
pH	7.46 (0.05)	7.47 (0.04)	7.48 (0.05)
Bicarbonate, mEq/L	28 (2)	29 (2.3)	28 (1.9)
Lactate, mmol/L	1.4 (1.1)	1.0 (0.2)	1.2 (0.5)

*Data are presented as mean (SD).

Analyzer; GE, Boulder, CO). Instead we measured nitrotyrosine, a downstream, validated surrogate of nitric oxide formation.[19,20] Nitrotyrosine (Northwest Life Science Specialties, Vancouver, WA) was detected by enzyme-linked immunosorbent assay.

Animals were acclimated for 10 minutes before the experiment, and then isoflurane was reduced to 1.5%. The animals were then randomized to one of 3 arms: hydroxocobalamin, hydroxocobalamin+sodium thiosulfate, or sodium thiosulfate. A 4% potassium cyanide mixture (potassium cyanide; Sigma Aldrich, St. Louis, Missouri; normal saline solution) was infused continuously until severe hypotension developed, defined as a 50% reduction in baseline mean arterial pressure for 1 minute. In our previous experiments, we have found this dose effective in causing severe hypotension and 100% lethality if untreated while allowing animals to recover with antidotal treatment.[21]

When a 50% reduction in mean arterial pressure was achieved, the animals were administered hydroxocobalamin (150 mg/kg), hydroxocobalamin (150 mg/kg)+sodium thiosulfate (413 mg/kg), or sodium thiosulfate (413 mg/kg) intravenously during 10 minutes. Each animal received the antidote in an equal volume of 200 mL. The hydroxocobalamin was infused during 7.5 minutes and the sodium thiosulfate during 2.5 minutes.[11] The dose and infusion duration for hydroxocobalamin and sodium thiosulfate were based on our previous published model and other large-animal studies.[3,11,14] To ensure full antidotal effect, we used the maximal accepted doses of each antidote. Because we could not dose the medication according to effect, the entire dose was administered as an initial bolus.[3] Ten milliliters of saline solution was infused before and after each drug administration. Also at hypotension, FiO_2 was increased to 1.0, and a 20 mL/kg warmed (38°C) saline solution bolus was infused to replicate clinically relevant resuscitative treatments. The animals were then monitored for 60 minutes after severe hypotension was reached. Death was defined as a mean arterial pressure less than 20 mm Hg for 5 minutes. The animals were killed with intravenous administration of sodium pentobarbital 100 mg/kg.

Whole blood cyanide levels were measured with spectrophotometry at a referral laboratory (Diagnostic Center for Population and Animal Health, Michigan State University, Lansing, MI).[22] This method generates hydrogen cyanide gas, converts it to a cyanogen chloride, and uses spectrophotometric determination of the barbituric acid complex.[11,22] Plasma hydroxocobalamin and cyanocobalamin levels were measured with liquid chromatography and tandem mass spectrometry.[23]

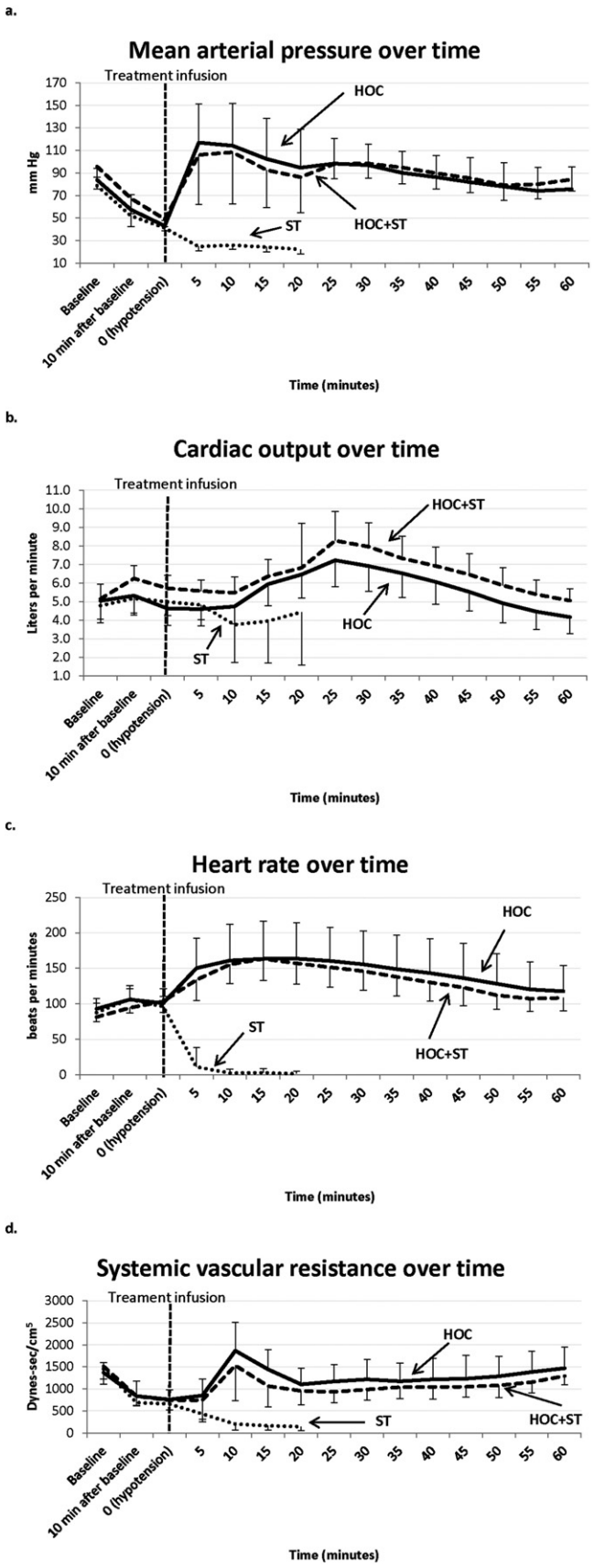
Methods of Measurement and Outcome Measures

The primary outcome measure was the change in mean arterial pressure after antidotal treatment from onset of hypotension (time zero) to 60 minutes. This outcome was defined before the study. We also compared cardiac output, pulse rate, mixed venous oxygenation, pH, lactate, base excess, serum bicarbonate, cyanide, and nitrotyrosine levels. Vital signs and hemodynamic measurements were recorded at 1-minute intervals and analyzed at 5-minute intervals. Serum blood sampling was conducted at baseline, 10 minutes after cyanide infusion start, at the onset of hypotension (50% of baseline mean arterial pressure), and at 10, 20, 30, 40, 50, and 60 minutes after hypotension.

Primary Data Analysis

Values for mean arterial pressure, the main outcome variables, were compared between groups from zero through 60 minutes with repeated-measures ANOVA. Animals that died before 60 minutes after hypotension were excluded from this analysis. Before beginning the study, we defined an increase in mean arterial pressure of 50% above the time zero value (hypotension) as clinically significant. According to a 50% difference in mean arterial pressure and an SD of 4.4 mm Hg derived from our previous studies, we calculated that we would need 12 animals in each group to provide a power of 90%, with an α of .05. Sample size calculations were performed with Stata (StatCorp, College Station, TX). Thirty-six animals were used, with the expectation of early death before conclusion of the experiment in 10% to 15% of the animals.

Secondary variables (cardiac output, pulse rate, systemic vascular resistance, and mixed venous oxygenation) were compared between groups at zero through 60 minutes with repeated-measures ANOVA also.



Values for arterial blood pH, lactate, cyanide, nitrotyrosine, bicarbonate, base excess, and potassium concentrations were compared between groups with repeated-measures ANOVA for zero to 60 minutes.

Post hoc analysis at individual times was performed with univariate analysis only if the multivariate test showed a significant difference between groups. Statistical significance was set at $P<.05$, and all P values represent 2-tailed calculations. Statistical analyses were performed with SSPS (version 16; SPSS, Inc., Chicago IL).

RESULTS

Characteristics of Study Subjects

At baseline, the groups had similar vital signs and biochemical variables (Table 1). At time zero, predefined as a reduction of mean arterial pressure to 50% of baseline, there were no significant differences between groups (Figure 1*A* to *D*) (Table 2).

Main Results

After reaching the toxic effect of hypotension (time zero), 1 animal in the hydroxocobalamin group, 2 animals in the hydroxocobalamin/sodium thiosulfate group, and all 12 animals in the sodium thiosulfate group died before completion of the experiment. Mortality in the sodium thiosulfate alone group (100%) was statistically different from that of the other groups ($P<.001$).

Of the animals that survived, mean arterial pressure, cardiac output, and pulse rate all trended toward baseline (Figure 1*A* to *D*). The change in mean arterial pressure was most noticeable immediately after hydroxocobalamin administration. At 10 minutes after hypotension, mean arterial pressure in the hydroxocobalamin group was 30 mm Hg (36%) greater than baseline values and in the hydroxocobalamin/sodium thiosulfate group was 12 mm Hg (13%) greater than baseline (Figure 1*A*). There were no differences in pulse rate or cardiac output between the hydroxocobalamin groups at zero to 60 minutes.

No difference was detected between hydroxocobalamin groups in regard to lactate, bicarbonate, pH, or cyanide levels from time zero through the end of the study (Figure 2*A* to *D*). Lactate (2.6 versus 2.1 mmol/L), pH (7.44 versus 7.42), and bicarbonate (25 versus 26 mEq/L) levels at 60 minutes were similar in the hydroxocobalamin groups. Cyanide levels were undetectable in both hydroxocobalamin groups by 10 minutes after hypotension.

Figure 1. Vital signs and hemodynamic measurements reported over time until the end of the experiment. Hydroxocobalamin group, N=11; hydroxocobalamin+sodium thiosulfate group, N=10. Baseline samples were drawn immediately before infusion of cyanide. *HOC,* Hydroxocobalamin; *ST,* sodium thiosulfate.

Table 2. Cyanide dosing and interval data at hypotension.*

Characteristics at Hypotension (MAP < 50% of Baseline)	Hydroxocobalamin (N=12)	Hydroxocobalamin+Sodium Thiosulfate (N=12)	Sodium Thiosulfate (N=12)
Cyanide dose, mg/kg	4.8 (2)	5.7 (2)	5 (0.8)
Time to hypotension, min:sec	27:40 (14:21)	33:59 (13:40)	24:56 (4:02)
MAP at hypotension, mm Hg	43 (5)	49 (6)	41 (2)
Lactate, mmol/L	6.5 (1)	7.6 (0.2)	8 (0.5)
Cyanide level, μg/mL	3.4 (0.7)	3.4 (0.9)	3.9 (1)
pH	7.42 (0.1)	7.41 (0.1)	7.4 (0.1)

MAP, mean arterial pressure.
*Data are presented as mean (SD).

Nitrotyrosine levels were similar at baseline (hydroxocobalamin 4.7 nM, hydroxocobalamin/sodium thiosulfate 2.3 nM, sodium thiosulfate 2.6 nM; $P=.70$). Levels increased by more than 60% at hypotension in all groups. In the hydroxocobalamin groups, nitrotyrosine levels decreased significantly after hydroxocobalamin infusion. In the sodium thiosulfate group, nitrotyrosine levels increased from baseline until death.

LIMITATIONS

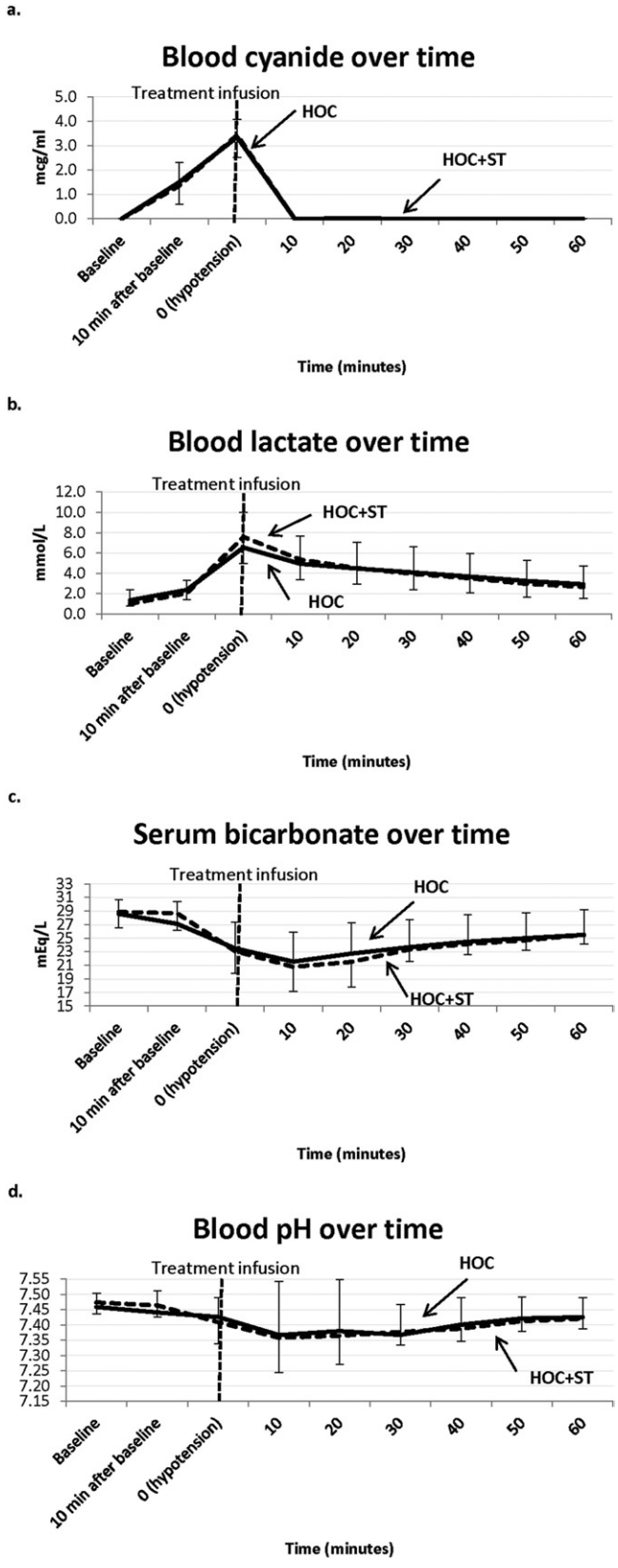
There were several limitations to our study. The primary limitation is that an animal model does not precisely reproduce human toxicity. We chose a swine model because it has been used in previous investigations of cyanide toxicity and because the swine cardiovascular system is analogous to that of humans.[11,24,25] We used maximal doses of each antidote to achieve maximal effects. Lower doses of the antidotes may have provided different outcomes. Another limitation is the use of intravenous cyanide as a substitute for the more common exposure of inhalational exposure. Both have rapid onset, but the intravenous route provided a more controlled way of inducing toxicity without the large loss of life that might be associated with the relatively uncontrolled absorption through an inhalational model of cyanide poisoning. We addressed this concern by establishing a clinical, objective endpoint (reduction of mean arterial pressure) and by measuring cyanide levels to ensure that toxic concentrations similar to those observed in humans were achieved. In addition, the inhalational route could put the research staff at a greater risk than the intravenous route because of undetected leaks in the ventilation system.[13,14] We used potassium cyanide; however, the potassium dose infused was small. The 50-kg animals received 2 mEq of potassium in approximately 30 minutes. Finally, observing the animals for a longer period may have shown a difference between the hydroxocobalamin and hydroxocobalamin/sodium thiosulfate groups. Last, we did not study the effects of our treatments on cyanide-induced respiratory failure, which may be a model of an early sign of moderate cyanide toxicity.

DISCUSSION

Sodium nitrite and sodium thiosulfate are often used together as part of a cyanide antidote kit. Sodium nitrite can cause hypotension and induced methemoglobinemia; thus, many authorities recommend not using it, particularly after structural fires.[3,6] As a result, sodium thiosulfate has been used as a single agent for cyanide toxicity, and positive case reports have been published.[8,26,27] Although the research into sodium thiosulfate has yielded conflicting results, its effectiveness as a preventive agent in cyanide toxicity has also been supported, and some older animal studies have supported its use as a sole agent.[10] Two studies concluded that sodium thiosulfate may be as effective as hydroxocobalamin.[16,28] Because it has few adverse effects, it is attractive as a possible antidote for cyanide toxicity, and recently several experts have stated that a direct comparison of sodium thiosulfate with hydroxocobalamin is needed.[4,5,12]

The combination of sodium thiosulfate with hydroxocobalamin has also been supported.[29] Hydroxocobalamin can bind cyanide and form the nontoxic cyanocobalamin, and sodium thiosulfate acts as a sulfur donor to detoxify cyanide to thiocyanate, a nontoxic, renally eliminated compound. Theoretically, the drugs would act synergistically. This combination is used in Europe, and several case reports have been published.[29-32] Studies also support their use as a combination.[4,27] In our previous study evaluating the efficacy of hydroxocobalamin and sodium thiosulfate versus sodium nitrite with sodium thiosulfate, we found that the groups had comparable mortality rates but that the hydroxocobalamin and sodium thiosulfate group experienced a faster return to baseline mean arterial pressure.[11] However, we could not find published reports of the comparison between hydroxocobalamin and hydroxocobalamin with sodium thiosulfate in a clinically relevant cyanide toxic model.

In the present study comparing the efficacy of sodium thiosulfate alone or in addition to hydroxocobalamin to reverse acute severe cyanide toxicity, we found that sodium thiosulfate alone was ineffective and resulted in 100% mortality when used as a single agent. There was no difference detected in mortality between hydroxocobalamin groups, and the rates were similar to those of our previous studies, validating the reproducibility of our model.[11,33] We also measured other biomarkers of antidotal effectiveness. Cyanide levels increased similarly in all 3 arms and were similar to those of our previous studies.[11,33] In both hydroxocobalamin arms, cyanide levels were undetectable after hypotension through the end of the study. In addition, lactate,



bicarbonate, and pH values were abnormal at hypotension and improved through the end of the study.

A unique aspect of our study is the measurement of nitrotyrosine levels as a surrogate for nitric oxide.[19,20] We could not measure nitric oxide directly because hydroxocobalamin's orange color interfered with our chemiluminescent assay used to measure nitric oxide. Hydroxocobalamin is a nitric oxide scavenger and therefore may exert beneficial effect through this mechanism; however, previous reports describing the effects of nitric oxide and hydroxocobalamin were not in a cyanide toxic model.[34,35] Nitric oxide release has been postulated to cause the initial hypotension detected in cyanide toxicity, and we observed an increase in nitrotyrosine level that paralleled the blood cyanide level increase.[36] All 3 of our treatment groups demonstrated an increase in nitrotyrosine level until hypotension. In the sodium thiosulfate group, we detected a continued increase in nitrotyrosine level until the animal was killed. In both hydroxocobalamin groups, we detected a dramatic decrease in nitrotyrosine levels after hydroxocobalamin administration. We observed an inverse relationship throughout the study between mean arterial pressure and nitrotyrosine levels in all groups, suggesting that nitric oxide may mediate blood pressure effects of cyanide and that hydroxocobalamin may exert its antidotal effect partially through nitric oxide scavenging.

As occurred in previous studies, the blood pressure initially increased markedly after hydroxocobalamin administration but then decreased over time, returning to baseline by the end of the experiment. A longer observation period may be valuable but was beyond the scope of our study, which focused on the initial resuscitation from cyanide toxicity. The mild acidosis observed at hypotension was expected because the lactic acidosis from cyanide does not directly cause the acidemia,[2,37] which is an additive effect of hypoperfusion, respiratory failure, and a direct cyanide toxic effect on cellular respiration.

According to our study results, sodium thiosulfate alone is not effective for cyanide-induced hypotension and resulted in 100% mortality in our model. The addition of sodium thiosulfate to hydroxocobalamin did not improve mortality, hemodynamic values, or biochemical markers such as lactic acidosis, acidemia, or cyanide levels. In addition, if infused improperly, the combination may reduce hydroxocobalamin's effectiveness.[26] Sodium thiosulfate has few adverse effects, but vomiting, arthralgias, and injection site pain have been reported in humans.[7,26,38,39] In addition, animal studies have reported a higher mortality with sodium thiosulfate administered alone.[7,26] Although there may a theoretic benefit of using hydroxocobalamin with sodium thiosulfate, previous studies have not been rigorous or have not used a critically ill, clinically

Figure 2. Cyanide levels and laboratory values reported over time until the end of the experiment. Hydroxocobalamin group, N=11; Hydroxocobalamin+sodium thiosulfate group, N=10.

relevant model. According to our results, hydroxocobalamin is effective when administered alone.

In conclusion, sodium thiosulfate failed to reverse cyanide-induced shock in our swine model of severe cyanide toxicity. Further, sodium thiosulfate was not found to be efficacious when added to hydroxocobalamin in the treatment of cyanide-induced shock. Hydroxocobalamin alone was found to be effective for severe cyanide toxicity.

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