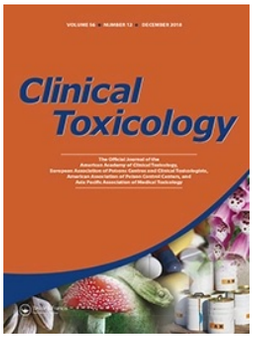

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BASIC RESEARCH

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Intramuscular sodium tetrathionate as an antidote in a clinically relevant swine model of acute cyanide toxicity

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ABSTRACT

Background: Cyanide is a metabolic poison used in multiple industries and is a high threat chemical agent. Current antidotes require intravenous administration, limiting their usefulness in a mass casualty scenario. Sodium tetrathionate reacts directly with cyanide yielding thiosulfate and the non-toxic compound thiocyanate. Thiosulfate, in turn, neutralizes a second molecule of cyanide, thus, per mole, sodium tetrathionate neutralizes two moles of cyanide. Historical studies examined its efficacy as a cyanide antidote, but it has not been evaluated in a clinically relevant, large animal model, nor has it previously been administered by intramuscular injection.

Objective: The objective of this study is to evaluate the efficacy of intramuscular sodium tetrathionate on survival and clinical outcomes in a large, swine model of severe cyanide toxicity.

Methods: Anesthetized swine were instrumented for continuous monitoring of hemodynamics, then acclimated and breathing spontaneously prior to potassium cyanide infusion (0.17 mg/kg/min). At 6-min post-apnea (no breaths for 20 s), the cyanide infusion was terminated, and animals were treated with sodium tetrathionate (~18 mg/kg) or normal saline control. Clinical parameters and laboratory values were evaluated at various time points until death or termination of the experiment (90 min post-treatment).

Results: Laboratory values, vital signs, and time to apnea were similar in both groups at baseline and treatment. Survival in the sodium tetrathionate treated group was 100% and 17% in controls ($p = 0.0043$). All animals treated with sodium tetrathionate returned to breathing at a mean time of 10.85 min after antidote, and all but one control remained apneic through end of the experiment. Animals treated with tetrathionate showed improvement in blood lactate ($p \leq 0.002$) starting at 30 min post-treatment. The average time to death in the control group is 63.3 ± 23.2 min. No systemic or localized adverse effects of intramuscular administration of sodium tetrathionate were observed.

Conclusion: Sodium tetrathionate significantly improves survival and clinical outcomes in a large, swine model of acute cyanide poisoning.

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Cyanide poisoning; sodium tetrathionate; terrorism; potassium cyanide; swine; intramuscular

Introduction

Cyanide is a rapid-acting metabolic poison and a high threat agent as recognized by the US Department of Homeland Security (DHS) [1]. It is also widely used in industrial settings such as mining and in gold extraction from mineral ore [2]. Exposures can occur following smoke inhalation, dermal absorption, or ingestion resulting in adverse health effects within minutes [3]. A primary mechanism of cyanide toxicity is inhibition of cellular respiration by binding cytochrome C oxidase causing lactic acidemia, apnea, hypotension, coma, and death [4]. While there are efficacious cyanide antidotes such as hydroxocobalamin, sodium nitrite, and sodium thiosulfate, these antidotes must be administered intravenously in large volumes, making their use in a mass casualty scenario limited [5]. Moreover, there are additional limitations to these antidotes. For example, sodium nitrite can cause methemoglobinemia, cyanmethemogobinemia, and hypotension secondary to the release of nitric acid [6]. The use of thiosulfate is limited due to its slow onset of action and hydroxocobalamin is expensive and has known interference with lab test making some results uninterpretable or inaccurate [5,7]. Given the high risk for a large-scale exposure, a safe, cost effective, rapid acting, small volume, and easy to administer antidote is needed for acute cyanide toxicity in humans. [8].

Sodium tetrathionate was used in the 1930s to treat thromboangiitis obliterans [9,10]. It was found to have minor adverse effects in chronic dosing at 400–900 mg including transient episodes of faintness, nausea, abdominal

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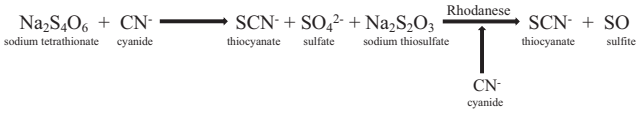

Figure 1. Reaction of sodium tetrathionate with cyanide. Sodium tetrathionate reacts with cyanide to form thiocyanate, sulfate, and sodium thiosulfate. Sodium thiosulfate acts as a substrate for the enzyme rhodanese and reacts with another molecule of cyanide (CN^-) to form thiocyanate (SCN^-), and sulfite (SO_3^{2-}). Sodium tetrathionate: $Na_2S_4O_6$; cyanide: CN^-; thiocyanate: SCN^-; sulfate: SO_4^{2-}; sodium thiosulfate: $Na_2S_2O_3$; sulfite: SO_3^{2-}.

discomfort, or weakness [9,10]. Safety studies in rabbits (50 mg/kg) and dogs (125 mg/kg) resulted in acute renal failure, a condition shown to be fully and rapidly reversible when treated [11,12]. In a separate human safety study, 30 participants received 600 mg of sodium tetrathionate twice daily for 1 week, and renal function was assessed [13,14]. The Mosenthal renal test was normal, but phenolsulphonphthalein excretion decreased by approximately 6% indicating a possible mild reduction in renal function [13,14].

In their *in vitro* studies, Baskin and Kirby demonstrated tetrathionate has inhibitory effects on rhodanese [15]. They found the conversion of cyanide to thiocyanate was inhibited in the presence of millimolar concentrations of tetrathionate. However, they suggested *in vivo,* these inhibitory effects may not be seen due to extramitochondrial metabolism of tetrathionate into two moles of thiosulfate [15]. Thus, Baskin and Kirby conclude it is likely the antidotal effects of tetrathionate result from enzymatic and non-enzymatic conversion of cyanide to thiocyanate.

Either of the two sulfane sulfurs of sodium tetrathionate, $Na_2S_4O_6$, can react directly with cyanide, yielding thiocyanate, sulfate, and sodium thiosulfate. Thiosulfate, in turn, acts as a substrate for the enzyme rhodanese, again generating thiocyanate. Tetrathionate thereby neutralizes two moles of cyanide, compared to thiosulfate (Figure 1) [16–18]. Sodium tetrathionate was first examined in 1910 in a study indicating efficacy in a rabbit model of cyanide toxicity [19]. It was later shown to be 1.5–3.3 fold more potent then thiosulfate in treating mice, rats, and dogs with cyanide poisoning. These studies lacked proper controls and were done in animal models not clinically relevant by today's standards [20–22]. Thus, these early studies indicate sodium tetrathionate is minimally toxic and efficacious against cyanide toxicity [20–22]. Based on these data and tetrathionate's ability to neutralize two cyanide molecules, we hypothesized it would be efficacious against cyanide poisoning when delivered intramuscularly (IM) following cyanide exposure. The objective of our study was to evaluate the efficacy of IM sodium tetrathionate compared to saline control on survival and clinical outcomes in swine after acute systemic cyanide poisoning.

Study design

We conducted a randomized control trial comparing IM sodium tetrathionate to IM saline following acute cyanide toxicity in swine, a model commonly used to evaluate medical countermeasures to toxic chemical that cannot be tested in humans [20–22]. All experiments were approved by the University of Colorado's Institutional Animal Care and Use Committee (IACUC) and complied with the regulations and guidelines of the Animal Welfare Act and the American Association for Accreditation of Laboratory Animal Care. Animals were housed in and experimentation took place in an animal care facility.

Materials and methods

Sodium tetrathionate was purchased from Sigma Aldrich (St. Louis, MO). A 2 M solution was prepared by dissolving 3.06 g solid sodium tetrathionate in 5 ml sterile water immediately prior to use.

Animal subjects

Adolescent female Yorkshire swine (*Sus scrofa)* (Midwest Research Swine, Gibbon, MN) weighing 45–55 kg were used. Induction of anesthesia was accomplished with 10–20 mg/kg intramuscular injection of ketamine (MWI, Boise, ID) and 1–3% isoflurane (MWI, Boise, ID) via nosecone. Animals were intubated with a cuffed 8.0 mm endotracheal tube (Teleflex, Morrisville, NC), a peripheral auricular venous catheter placed, and a one-time bolus (7.5 ml/kg) of warm saline (B. Braun, Bethlehem, PA) was administered. A Drager Apollo anesthesia machine (Drager, Houston, TX) was used to maintain sedation with 1–3% isoflurane and 0.4 FiO_2. Tidal volume was set at 8 ml/kg and a respiratory rate of 16–20 breaths per minute, adjusting the minute volume to maintain an end-tidal CO_2 of 45–55 mm Hg. EKG electrodes, a pulse oximetry sensor, and a rectal temperature probe were placed. The external jugular vein and femoral artery were accessed via ultrasound-guided percutaneous micropuncture using the M9 Ultrasound system (Mindray, Mahwah, NJ) and a one-time bolus of heparin (100 units/kg) was given. Arterial blood pressure was continuously monitored via the femoral artery using a Transpac IV pressure transducer (ICU Medical, San Clemente, CA). Arterial blood pressure, pulse rate, oxygen saturations, end-tidal CO_2, body temperature, and respiratory parameters were monitored continuously and recorded every minute using the Drager Infinity Delta monitor and Patient Watch software, respectively. Following vascular access, isoflurane was weaned to 0.8–1% and 0.21 FiO_2 until the animal was breathing spontaneously, without mechanical ventilation as indicated by capnography (Scio Four, Drager, Houston, TX). Sedation was maintained with isoflurane throughout the experiment to minimize pain and discomfort as required by our IACUC.

Experimental procedures

Animals were acclimated for 10 min, as indicated by respiratory rate, blood pressure, heart rate, and pulse oximetry, then randomized to one of two groups: IM normal saline (six animals) or IM sodium tetrathionate (six animals). 61.4 millimolar (0.4%) solution of potassium cyanide (Sigma Aldrich, Saint Louis, Missouri) was infused into the jugular vein at a rate of 0.17 mg/kg/min until 6 min after apnea, defined as a

cessation of breathing for 20 s as determined by capnography. At this point, the infusion was turned off and the animals were injected with either 1.5 ml normal saline or 1.5 ml 2 M (~18 mg/kg) sodium tetrathionate in the semitendinosus muscle using a 1.5 inch 22 gauge needle. Animals were monitored for 90 min after treatment or until death, defined as a MAP less than 30 mm Hg for 10 continuous minutes [23–25].

Outcome measures

The primary outcome was rate of survival and time to death between groups following treatment. Physiological variables assessed were return to spontaneous ventilation following apnea, pulse rate, oxygen saturation, respiratory rate, blood pressure, and arterial blood gas; serum lactic acid, blood chemistries, and blood cyanide concentrations were also measured.

Euthanasia

At the end of the study, all animals were euthanized with an intravenous administration of 100 mg/kg sodium pentobarbital according to the regulations and guidelines of the Animal Welfare Act and the American Association for Accreditation of Laboratory Animal Care.

Data analysis

Prism 7.0 (GraphPad, La Jolla, California) was used for statistical analysis. Power analysis was used to determine sample size. An anticipated sample size of 6 per group was determined using an alpha of 0.05 and a power of 0.80, estimating a 70% difference in survival between groups.

Values are expressed as mean ± standard deviation. An unpaired *t*-test with Welch's correction was used to calculate 95% confidence intervals, means, and standard deviations. A two-tailed *t*-test was used for comparison between groups. A *p* value of less than 0.05 was considered significant. Survival between groups was analyzed by generating a Kaplan–Meier survival curve and comparing percent survival between groups using log-rank, Mantel–Cox analysis.

Results

Physiological and laboratory parameters were similar between control and treated groups at baseline and at the time of apnea (Tables 1 and 2). The time and amount of administered cyanide required to reach apnea were similar between groups, as was the amount of cyanide at the time of treatment (Table 2).

Animals receiving IM sodium tetrathionate showed significantly improved survival (6/6, $p = 0.0043$) compared to the control group (1/6) at 90 min post-treatment (Figure 2). All animals treated with sodium tetrathionate returned to breathing (37 ± 6 breaths/min) at 10.85 ± 1.64 min, whereas only one control animal returned to breathing (43 breaths/min) at 29 min. Laboratory parameters were also improved in sodium tetrathionate treated animals compared to the control group (Table 3). The blood cyanide concentration increased until the time of treatment. Following treatment, the blood cyanide concentration returned to baseline more rapidly in the sodium tetrathionate treated group compared to the control group (Figure 3). Blood lactate was significantly lower in sodium tetrathionate-treated animals by 30 min post-treatment ($p \leq 0.002$). (Table 3; Figure 3). There was no significant difference at 90 min post tetrathionate treatment in blood urea nitrogen (5.33 ± 1.86 vs. 6.33 ± 1.37,

Table 1. Physiological parameters at baseline of swine treated with sodium tetrathionate or saline control.

	Control $n = 6$	Sodium tetrathionate $n = 6$	Difference between means	95% CI difference
Weight (kg)	51.8 ± 3.3	49.6 ± 2.1	−2.2 ± 1.6	−5.8, 1.4
Lactate (mmol/L)	1.24 ± 0.22	0.88 ± 0.35	−0.36 ± 0.18	−0.77, 0.06
SBP (mm Hg)	109 ± 15.5	100 ± 15.4	−9 ± 8.9	−28.9, 10.9
MAP (mm Hg)	89 ± 15.4	80 ± 13.9	−9.0 ± 8.5	−27.9, 9.9
Pulse rate (beats per minute)	80 ± 10.2	87 ± 14.2	6.7 ± 7.2	−9.5, 22.8
Respiratory rate (breaths per minute)	31 ± 6.2	35 ± 8.1	3.8 ± 4.2	−5.6, 13.3

There is no significant difference in animal weight, laboratory values, hemodynamics, or respiratory rate at baseline. Data are presented as means ± standard deviation.
kg: kilogram; mmol/L: millimole/liter; mm Hg: millimeters of mercury; CI: confidence interval.

Table 2. Physiological parameters at apnea of swine treated with sodium tetrathionate or saline control.

	Control $n = 6$	Sodium tetrathionate $n = 6$	Difference between means	95% CI difference
KCN mg/kg at apnea	1.04 ± 0.34	1.01 ± 0.33	−0.03 ± 0.19	−0.46, 0.40
KCN mg/kg at treatment	1.98 ± 0.30	2.03 ± 0.33	−0.06 ± 0.18	−0.35, 0.46
Time to apnea (minutes)	6.12 ± 2.00	5.94 ± 1.93	−0.18 ± 1.14	−2.74, 2.34
Lactate (mmol/L)	2.39 ± 1.04	1.81 ± 0.66	−0.58 ± 0.50	−1.73, 0.57
pH	7.38 ± 0.05	7.39 ± 0.04	−0.01 ± 0.03	−0.05, 0.03
SBP (mm Hg)	94 ± 26.9	84 ± 19.1	−10.0 ± 13.5	−40.4, 20.4
MAP (mm Hg)	68 ± 21.5	61 ± 16.7	−7.0 ± 11.1	−32.0, 18.0
Pulse rate (beats per minute)	90 ± 11.0	94 ± 13.7	4.3 ± 7.2	−11.8, 20.4

There is no significant difference in total dose of KCN, time to apnea, laboratory values, or hemodynamics at apnea. Data are presented as means ± standard deviation.
KCN: potassium cyanide; mg/kg: milligram/kilogram; mmol/L: millimole/L; mm Hg: millimeters of mercury; CI: confidence interval.

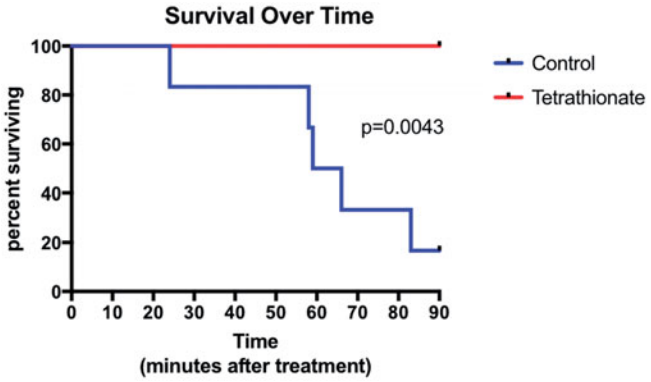

Figure 2. Percent survival in swine treated with intramuscular sodium tetrathionate as compared to saline control. Survival is improved with IM sodium tetrathionate administration following acute cyanide toxicity compared to saline controls. *p* value determined by log rank (Mantel–Cox) test, for comparison, *p* value less than or equal to 0.05 considered significant.

(CI −1.13, 3.13) or creatinine (1.60 ± 0.33 vs. 1.82 ± 0.29 (CI −0.18, 0.61) compared to baseline. Additionally, animals in the sodium tetrathionate treatment group showed improvement, though not statistically significant, in physiological parameters compared to controls including systolic blood pressure, mean arterial pressure, pulse rate, respiratory rate, and oxygen saturations (Table 3; Figure 4). The mean time to death in the control group was 63.3 ± 23.2 min, (CI difference 2.28, 51.05) following intramuscular administration of saline control.

Discussion

In a swine model of acute cyanide poisoning, IM sodium tetrathionate improved survival, laboratory parameters, and physiological outcomes compared to control animals. All

Table 3. Animal characteristics at death or end of the study of swine treated with sodium tetrathionate or saline control.

	Control $n = 6$	Sodium tetrathionate $n = 6$	Difference between means	95% CI difference
Time to death (minutes)	63.33 ± 23.24	90.00 ± 0	26.67 ± 9.49	2.28, 51.05
Lactate (mmol/L)	15.03 ± 3.83	6.21 ± 2.38	−8.82 ± 1.84	−13.04, −4.61
pH	7.03 ± 0.24	7.39 ± 0.06	0.35 ± 0.10	0.10, 0.60
Systolic blood pressure (mm Hg)	39 ± 27	81 ± 14	42 ± 12.5	12.8, 71.2
Mean arterial pressure (mm Hg)	28 ± 21	53 ± 11	26 ± 9.5	3.2, 47.8
Heart rate (beats per minute)	30 ± 73	134 ± 35	104 ± 33.1	26.2, 181.8
Pulse oximetry (% oxygen)	17 ± 20.0	84 ± 14.3	66.8 ± 10.0	44.2, 89.5

Animals in the sodium tetrathionate treatment group return to breathing following apnea, whereas 5/6 control animals do not. Sodium tetrathionate treatment results in increased survival time, improved blood lactate and pH, improved hemodynamics, pulse oximetry, and respiratory rate. Comparisons made at death/end of study due to control animals dying prior to the end of study. Data are presented as means ± standard deviation.
mmol/L: millimole/liter; mm Hg: millimeters of mercury; CI: confidence interval.

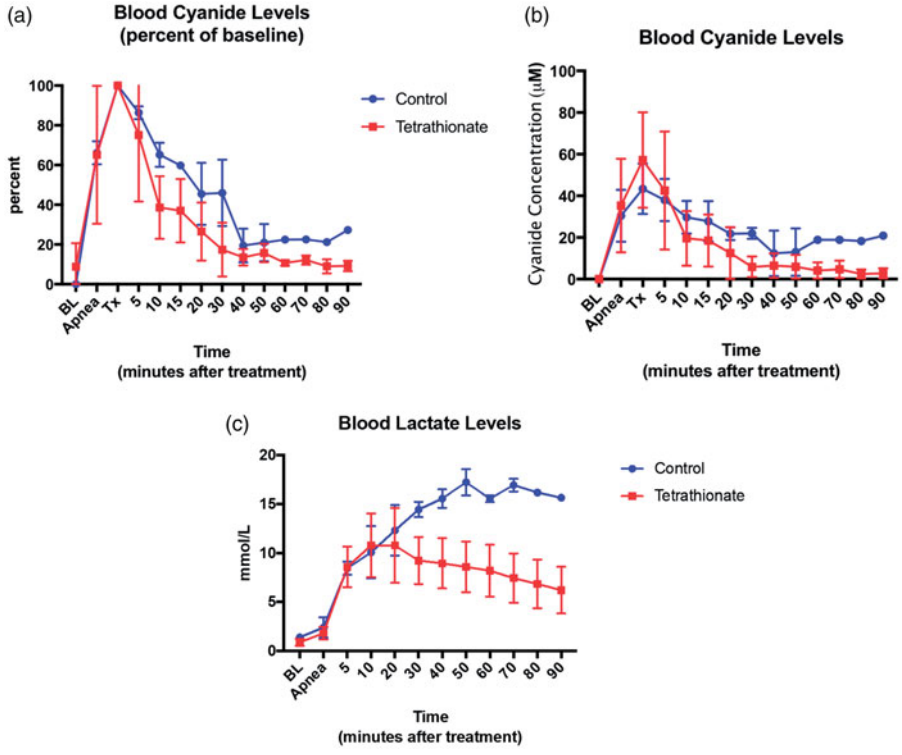

Figure 3. Laboratory parameters over time between the swine treated with sodium tetrathionate and control. (a–c) Blood cyanide concentrations increase until treatment, then return to baseline more rapidly in the sodium tetrathionate treatment than controls. Lactate is significantly improved starting at 30 min ($p \leq 0.002$) after treatment with sodium tetrathionate compared to controls over time. Data are presented as means ± standard deviation. Statistical comparisons could not be done at 80 and 90 min due to only one animal remaining in the control arm. mmol/L: millimoles/liter; mg/dL: milligrams/deciliter.

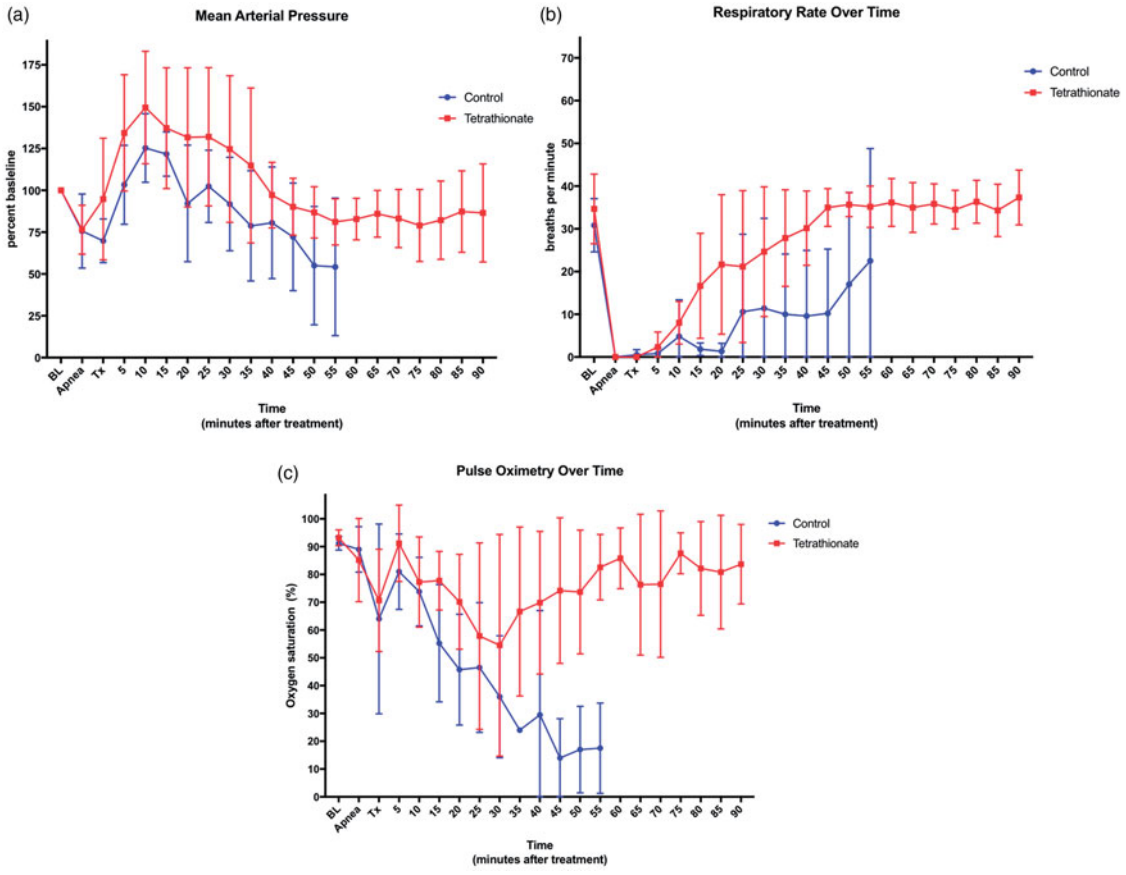

Figure 4. Clinical outcomes over time between the swine treated with sodium tetrathionate and control. (a–c) Mean arterial pressure, respiratory rate, and pulse oximetry are improved in sodium tetrathionate treated animals compared to controls. Mean arterial pressure shown as percent of baseline. Respiratory rate is significantly improved 10 ($p = 0.02$), 20, ($p = 0.03$), and 40 ($p = 0.04$) minutes post-treatment with sodium tetrathionate compared to controls over time. Pulse Oximetry is significantly improve in the sodium tetrathionate group at 50 ($p = 0.04$) and 60 ($p = 0.02$) min after treatment compared to controls. Data are presented as means ± standard deviation. Statistical comparisons could not be done at 80 and 90 min due to only one animal remaining in the control arm. mm Hg: millimeters of mercury.

animals treated with sodium tetrathionate (6/6) returned to breathing and survived for the entire study, whereas only 1 animal in the control group survived (1/6). Significant improvement occurred in blood lactate and pH in the sodium tetrathionate-treated group compared to saline controls. Sodium tetrathionate improved physiological parameters as indicated by arterial blood pressure, pulse rate, respiratory rate, and oxygen saturations.

Since cyanide toxicity studies cannot be done in humans, they must be performed in live animals. The large swine model we used allows for accurate continuous monitoring of hemodynamic and physiological parameters indicative of severe toxicological effects of cyanide, allowing us to more accurately determine antidote efficacy and therapeutic effects. While the time to death in this model may seem to reflect a less severe clinical poisoning compared to scenarios with rapid death, the swine model results in similar outcomes as seen with human cyanide poisoning, marked by apnea, hypotension, lactic acidemia, myocardial depression, and death. The efficacy of tetrathionate in a rapidly lethal model of cyanide poisoning was not evaluated in this model. The swine model also simplifies human dose scaling, as the allometric dose scaling between swine and humans is 1.1:1 [26].

Current FDA approved treatments for cyanide poisoning fall into one of three classes: methemoglobin generators and nitric oxide donors (sodium nitrite), sulfur donors (sodium thiosulfate), or direct binding agents (hydroxocobalamin) [27,28]. A unique quality of sodium tetrathionate compared to other cyanide antidotes is that cyanolysis yields thiosulfate, which then acts as a substrate for rhodanese, allowing it to further neutralize cyanide. The increased potency of sodium tetrathionate compared to other FDA approved antidotes allows it to be given in smaller volumes and intramuscularly, making it an ideal antidote for mass casualty exposures. Furthermore, since sodium tetrathionate has been used historically to treat thromboangiitis obliterans, significant data already exist regarding safety [9,10]. As written in the Introduction, this safety data indicated the potential for renal toxicity from large dose infusions. The tetrathionate dose that caused adverse effects in humans was a few hundred mg, which is similar to the antidotal dose of 18 mg/kg used in this study. Although the doses are similar, the adverse effects in humans occurred after repeated dosing.

The benefit of administering this dose to counteract lethal poisoning outweighs the potential adverse effects observed in past studies. Currently, tetrathionate is not commercially available, the safety data presented here are taken from historical studies that may not be applicable to today's regulatory standards; therefore, some additional safety data is still needed. Additional studies should be performed to evaluate sodium tetrathionate completely as a countermeasure for cyanide toxicity. Finally, as oral cyanide is a rising threat, evaluation of tetrathionate for oral cyanide ingestion would be important as a higher dose of cyanide with different pharmacokinetics generally occurs with oral ingestion than inhaled or intravenous cyanide [29,30].

Limitations

Our study does not exactly replicate human exposure to cyanide. First, animals are sedated to prevent pain and suffering, as required by our institutional IACUC. To minimize anesthesthetic effects, we use the lowest dose of isoflurane required (0.8–1%) to maintain sedation. Despite the low dose of anesthetics used, we appreciate there can be an impact on toxicodynamics; however, to circumvent this, we variable we use sedation in both the treatment and control group. Second, we infused cyanide intravenously. While we understand the majority of cases of cyanide exposure are from ingestion or inhalation, we opted for intravenous infusion to provide a controlled, consistent, and reproducible model of acute toxicity [4,24,25,31]. Future studies to evaluate the efficacy of sodium tetrathionate in other models of cyanide toxicity, including rapidly lethal models, are warranted. Lower doses of tetrathionate may prove to be beneficial in other models of exposure as the systemic absorption of cyanide might be delayed. It is also possible an increased dose of tetrathionate or a combination therapy might be needed to reverse rapidly lethal models of cyanide poisoning. Regardless of dose, thorough safety testing is needed. And finally, we use potassium cyanide; the dose of potassium is approximately 2 mEq over 30 min, which does not result in any detectable adverse cardiac effects.

The studies conducted were short term survival studies. While our animals did survive to 90 min post-treatment and laboratory, and clinical outcomes returned to near baseline, we do not know the long-term outcomes following treatment with sodium tetrathionate. However, the toxicological effects of cyanide are rapid, and we treated the animals within minutes of becoming apneic; therefore, we expect long-term effects to be minimal. Furthermore, we treated all animals at 6 min post-apnea. Studies evaluating the latest optimal treatment time should be conducted since in a mass casualty scenario it is unknown how long it will take emergency responders to reach the scene. However, in a mass casualty scenario, it is likely that some supportive care will be provided prior to antidote administration. Additionally, these studies did not compare efficacy of sodium tetrathionate to other antidotes currently being developed, such as cobinamide or dimethyltrisulfide. Future studies aimed at comparing efficacy or potentially combining antidotes, especially those with different mechanisms of action, are warranted.

Conclusion

Sodium tetrathionate administered by intramuscular administration significantly improved survival and clinical outcomes compared to saline in a large, swine model of acute cyanide poisoning.

Author contributions

TH, AE, PN, SM, MB, GB, and VB were involved in study design, manuscript review, and data analysis. TH, AE, PN, and VB were involved in experiment execution, data collection, statistical analysis, and manuscript generation. All authors reviewed and approved the manuscript for submission.

Disclosure statement

No potential conflict of interest was reported by the authors.

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