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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-minutes post apnea (no breaths for 20 seconds), the cyanide infusion was terminated, and animals 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 minutes post treatment).

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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 minutes after antidote, and all but one control remained apneic through end of the experiment. Animals treated with tetrathionate showed improvement in blood lactate (P≤0.002) starting at 30 minutes post treatment. The average time to death in the control group of 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.

Keywords

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 1930's 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 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 one 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 2 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, 17, 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, 21, 22]. Thus, these early studies indicate sodium tetrathionate is minimally toxic and efficacious against cyanide toxicity [20, 21, 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, 21, 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 grams 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 pressures 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 (6 animals) or IM sodium tetrathionate (6 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 sec 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, 24, 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 by 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 was 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 minutes. 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 minutes post tetrathionate treatment in blood urea nitrogen (5.33 ± 1.86 vs. 6.33 ± 1.37, (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 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 is 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.

Funding Sources/Disclosures:

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References

1. US Department of Homeland Security. Chemical Facility Anti-Terrorism Standards 2018 [cited 9/22/2018]. Available from: https://www.dhs.gov/appendix-a-chemicals-interest-list
2. Luque-Almagro VM, Moreno-Vivian C, Roldan MD. Biodegradation of cyanide wastes from mining and jewellery industries. Current opinion in biotechnology. 2016 4;38:9–13. doi: 10.1016/j.copbio.2015.12.004. eng. [PubMed: 26745356]
3. Egekeze JO, Oehme FW. Cyanides and their toxicity: a literature review. Tijdschrift voor diergeneeskunde. 1980 4 15;105(8):suppl 2:104–14. eng.
4. Bhandari RK, Oda RP, Petrikovics I, et al. Cyanide toxicokinetics: the behavior of cyanide, thiocyanate and 2-amino-2-thiazoline-4-carboxylic acid in multiple animal models. Journal of analytical toxicology. 2014 5;38(4):218–25. doi: 10.1093/jat/bku020. eng. [PubMed: 24711295]
5. Hall AH, Saiers J, Baud F. Which cyanide antidote? Critical reviews in toxicology. 2009;39(7):541–52. doi: 10.1080/10408440802304944. eng. [PubMed: 19650716]
6. Borron SW, Baud FJ. Antidotes for acute cyanide poisoning. Curr Pharm Biotechnol. 8 2012; 13(10): 1940–1948. doi.org 10.2174/138920112802273182. [PubMed: 22352728]
7. Carlsson CJ, Hansen HE, Hilsted L, Malm J, Odum L, Szeecsi PB. An evaluation of the interference of hydroxocobalamin with chemistry and co-oximetry tests on nine commonly used instruments. Scand J Clin Lab Invest. 9 2011;71(5):378–386. doi: 10.3109/00365513.2011.573573. [PubMed: 21495916]
8. Borron SW. The perfect antidote. Acad Emerg Med. 2014 11;21(11):1292–4. doi: 10.1111/acem.12505. eng. [PubMed: 25377413]

9. Theis FV, Freeland MR. Thromboangitis obliterans: Treatment with sodium tetrathionate and sodium thiosulfate. Arch Surg. 1940;40:190–207.
10. Theis FV, Freeland MR. Thrombo-angiitis obliterans: Clinical observations and arterial blood oxygen studies during treatment of the disease with sodium tetrathionate and sodium thiosulfate. Ann Surg. 1941;113(6):1107–1108. [PubMed: 17857827]
11. Sloan H Production of experimental uremia by sodium tetrathionate. Proc Soc Exp Biol Med 1951;76(2):344–346. [PubMed: 14827921]
12. Gilman APF. The metabolic reduction and nephrotoxic action of tetrathionate in relation to a possible interaction with sulfhydryl compounds. Am J Physiol. 1946;147:115–126. [PubMed: 21000729]
13. McDonald RH. The Value of the Urea Clearance Test. Cleveland Clinic Journal of Medicine.1936;3(2):127–133.
14. Bloom NFG, Policoff L. Toxicity of sodium tetrathionate. Proc Soc Exp Biol Med 1949;72(1):207–209. [PubMed: 15391715]
15. Baskin SI, Kirby SD. The effect of sodium tetrathionate on cyanide conversion to thiocyanate by enzymatic and non-enzymatic mechanisms. J Appl Toxicol. 1990 10;10(5):379–382. doi.org/10.1002/jat.2550100511. [PubMed: 2254590]
16. Ji C, Yan X, Horvath AK, et al. Comprehensive simultaneous kinetic study of sulfitolysis and thiosulfatolysis of tetrathionate ion: unravelling the unique pH dependence of thiosulfatolysis. The journal of physical chemistry A. 2015 2 26;119(8):1238–45. doi: 10.1021/jp5108119. eng. [PubMed: 25651337]
17. Eremenko RRK BA. Study of the reactions of the polythionates by means of tagged sulfur. Reactions of the tetrathionates and the pentathionates. 1955;25:1189–1196.
18. Kelly DP CL, Trundinger PA. Cyanolysis and spectrophotometric estimation of trithionate in mixture with thiosulfate and tetrathionate. Analytical Chemistry. 1969;41:898–901.
19. Versuche HJ. überentgiftung der blansäure durch schwefelabspaltende substanzen. Biochemische Zeitschrift. 1910;28:208–212.
20. Draize JH. Sodium tetrathionate and methylene blue in cyanide and carbon monoxide poisoning. Science (New York, NY). 1933 8 18;78(2016):145. doi: 10.1126/science.78.2016.145. eng.
21. Binet L, Wellers G, Dubrisay J. [Value and mechanism of the antidote action of sodium tetrathionate in hydrocyanic poisoning]. La Presse medicale. 1951 5 12;59(32):641–3. und. [PubMed: 14853831]
22. Nitescu II, Craiu R, Wassermann N. Cyan ides and anticyanides. The action of sodium tetrathionate as an antidote in hydrocyanic poisoning. Rumanian medical review. 1961;5:203–4. eng. [PubMed: 13729279]
23. Bebarta VS, Pitotti RL, Dixon P, et al. Hydroxocobalamin versus sodium thiosulfate for the treatment of acute cyanide toxicity in a swine (Sus scrofa) model. Ann Emerg Med. 2012 6;59(6):532–9. doi: 10.1016/j.annemergmed.2012.01.022. [PubMed: 22387086]
24. Bebarta VS, Pitotti RL, Boudreau S, et al. Intraosseous versus intravenous infusion of hydroxocobalamin for the treatment of acute severe cyanide toxicity in a Swine model. Acad Emerg Med. 2014 11;21(11):1203–11. doi: 10.1111/acem.12518. [PubMed: 25377396]
25. Bebarta VS, Tanen DA, Boudreau S, et al. Intravenous cobinamide versus hydroxocobalamin for acute treatment of severe cyanide poisoning in a swine (Sus scrofa) model. Ann Emerg Med. 2014 12;64(6):612–9. doi: 10.1016/j.annemergmed.2014.02.009. eng. [PubMed: 24746273]
26. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016 3;7(2):27–31. doi: 10.4103/0976-0105.177703. eng. [PubMed: 27057123]
27. Baskin SI, Brewer TG. Textbook of military medicine Part I, Warfare, weaponry, and the casualty Washington, D.C: Borden Institute, Walter Reed Army Medical Center Office of the Surgeon General, U.S. Army; U.S. Army Medical Dept. Center and School; U.S. Army Medical Research and Material Command; Uniformed Services University of the Health Sciences; 1997 (Sidell FRTE, Franz DR, Borden Institute (U.S.), editor. Medical aspects of chemical and biological warfare).
28. Cummings TF. The treatment of cyanide poisoning. Occupational medicine. 2004; 54(2): 82–85. [PubMed: 15020725]

29. Moore J ISIS Supporters Call for Poisoning of Food in Grocery Stores Across U.S. and Europe 2107 [cited 2018 August 2]. Available from: http://www.newsweek.com/isis-supporters-call-poisoning-grocery-stores-us-and-europe-660750

30. Hendry-Hofer TB, Witeof AE, Lippner D, Ng PC, Mahon SB, Brenner M, Rockwood GA, Bebarta VS. Intramuscular dimethyl trisulfide: Efficacy in a large swine model of acute severe cyanide toxicity. Clin Tox. 2018;11:1–6.

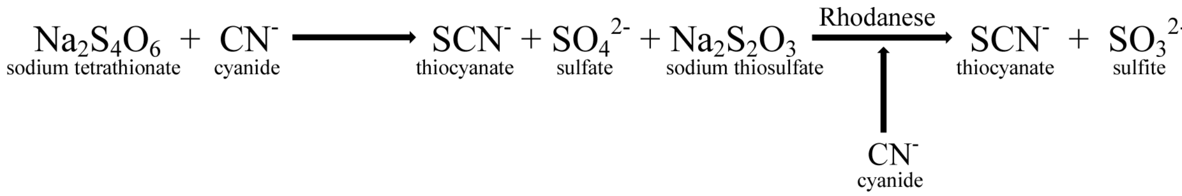

Figure 1.

Reaction of sodium tetrathionate with cyanide.

Figure 1. 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-}

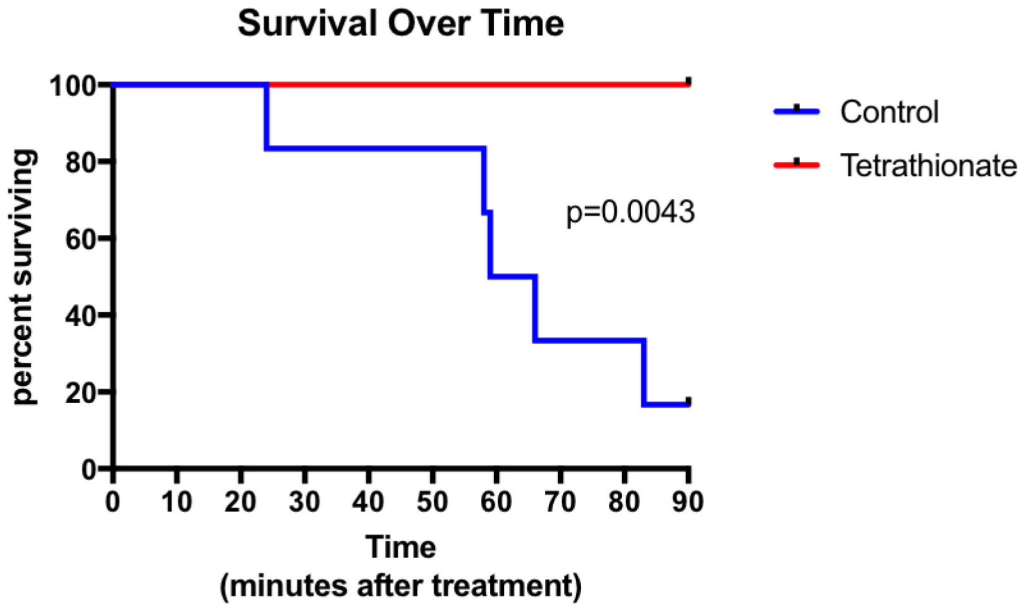

Figure 2.

Percent survival in swine treated with intramuscular sodium tetrathionate as compared to saline control

Figure 2. 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.

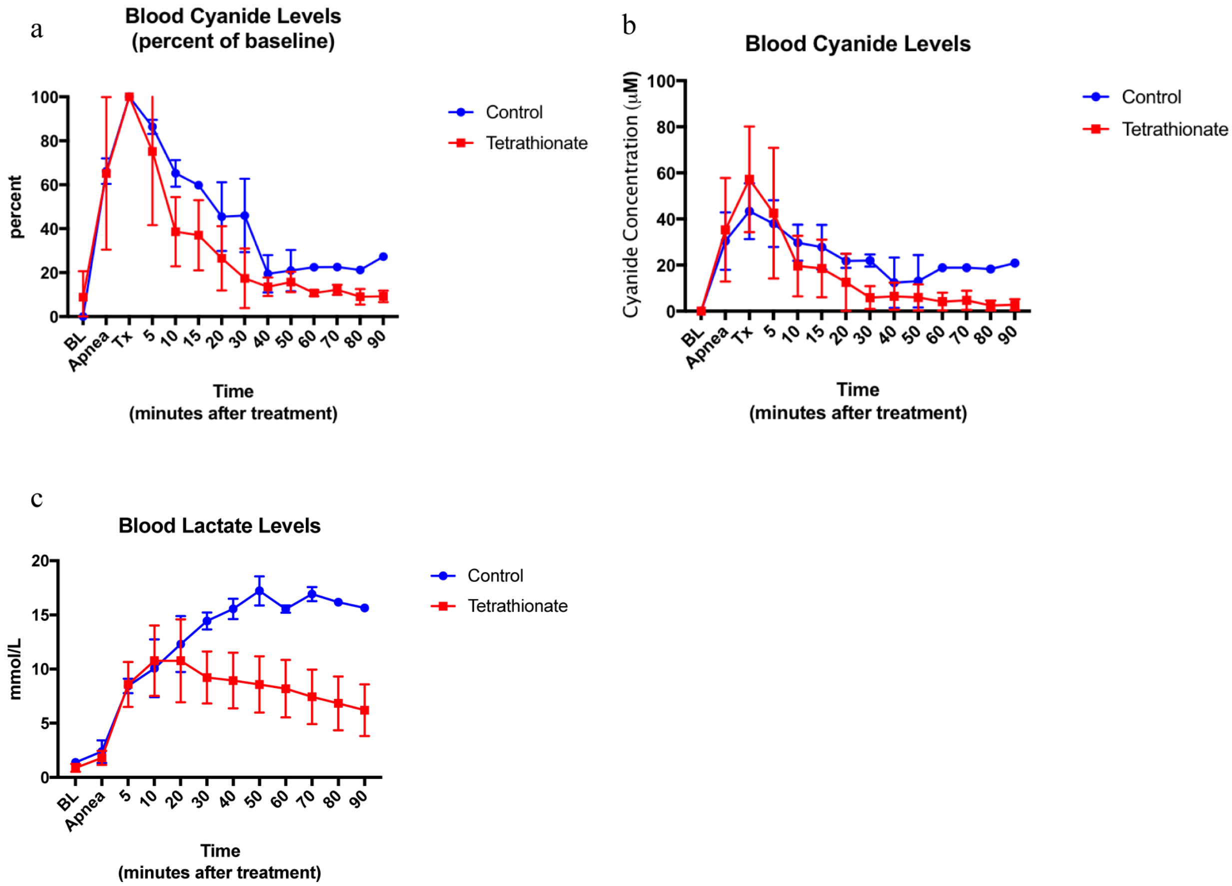

Figure 3.

Laboratory parameters over time between the swine treated with sodium tetrathionate and control

Figure 3a-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 minutes ($P \leq 0.002$) after treatment with sodium tetrathionate compared to controls over time.

Data is 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

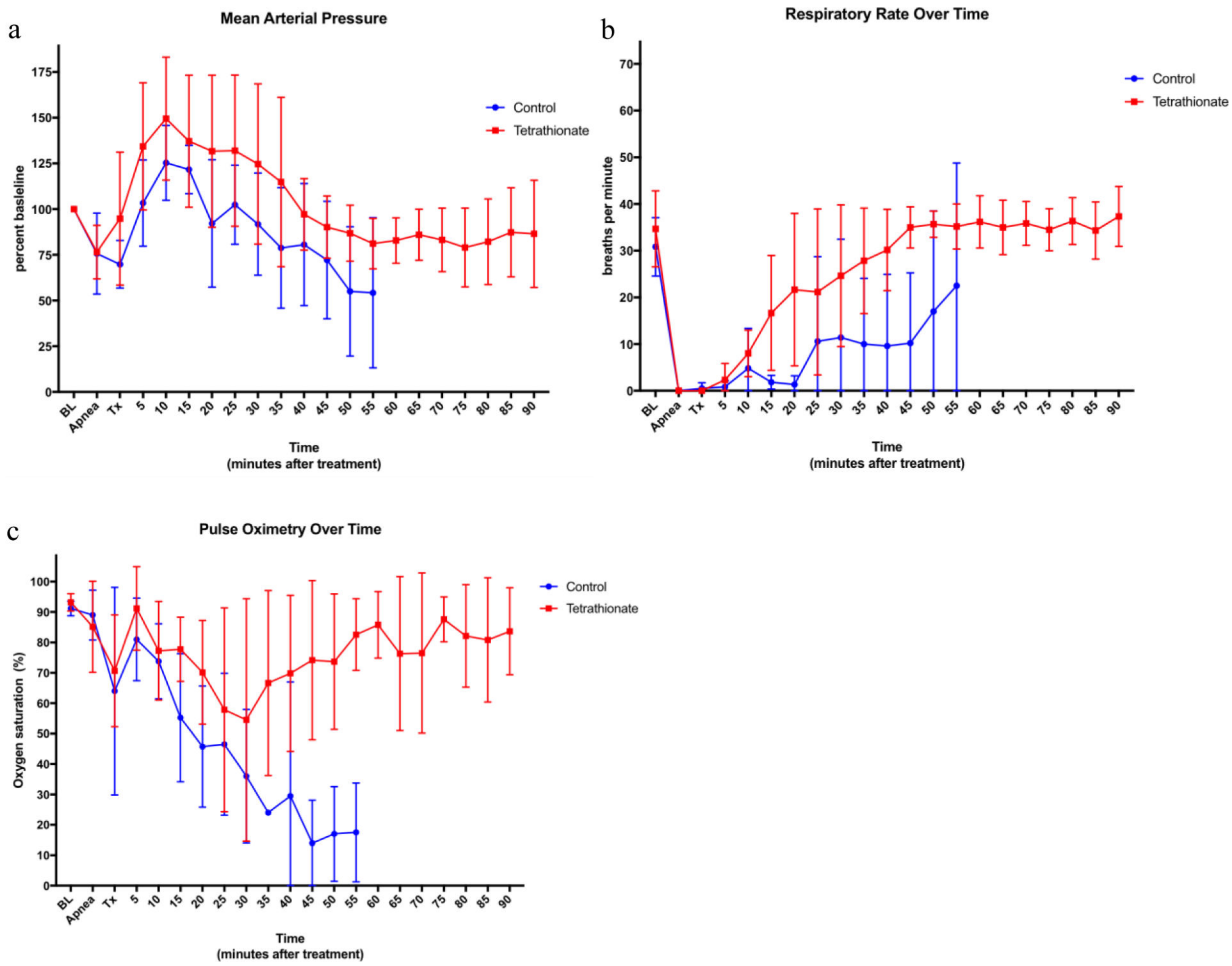

Figure 4.

Clinical outcomes over time between the swine treated with sodium tetrathionate and control Figure 4a-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), 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) minutes after treatment compared to controls.

Data is 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

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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

Table 1. There is no significant difference in animal weight, laboratory values, hemodynamics, or respiratory rate at baseline.

Data is 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

Table 2. There is no significant difference in total dose of KCN, time to apnea, laboratory values, or hemodynamics at apnea.

Data is presented as means ± standard deviation.

KCN: potassium cyanide; mg/kg: milligram/kilogram; mmol/L: millimole/L; mm Hg: millimeters of mercury; CI: confidence interval

Table 3.

Animal characteristics at death or end of 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

Table 3: 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 is presented as means ± standard deviation.

mmol/L: millimole/liter; mm Hg: millimeters of mercury; CI: confidence interval