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ORIGINAL ARTICLE

Efficacy of oral administration of sodium thiosulfate in a large, swine model of oral cyanide toxicity

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Abstract

Introduction Cyanide is a deadly poison, particularly with oral exposure where larger doses can occur before symptoms develop. Prior studies and multiple governmentagencies highlight oral cyanide as an agent with the potential for use in a terrorist attack. Currently, there are no FDA approved antidotes specific to oralcyanide. An oral countermeasure that can neutralize and prevent absorption of cyanide from the GI tract after oral exposure is needed. Our objective was toevaluate the efficacy of oral sodium thiosulfate on survival and clinical outcomes in a large, swine model of severe cyanide toxicity.

Methods Swine (45-55kg) were instrumented, sedated, and stabilized. Potassium cyanide (8 mg/kg KCN) in saline was delivered as a one-time bolus via an orogastric tube. Three minutes after cyanide, animals randomized to the treatment group received sodium thiosulfate (510 mg/kg, 3.25 M solution) via orogastric tube. Our primary outcome was survival at 60 minutes after exposure. We compared survival between groups by log-rank, Mantel-Cox analysis and trended labs and vital signs.

Results At baseline and time of treatment all animals had similar weights, vital signs, and laboratory values. Survival at 60 min was 100% in treated animals compared to 0% in the control group (p=0.0027). Animals in the control group became apneic and subsequently died by 35.0 min (20.2,48.5) after cyanide exposure. Mean arterial pressure was significantly higher in the treatment group compared to controls (p=0.008). Blood lactate (p=0.02) and oxygen saturation (p=0.02) were also significantly different between treatment and control groups at study end.

Conclusion Oral administration of sodium thiosulfate improved survival, blood pressure, respirations, and blood lactate concentrations in a large animal model of acute oral cyanide toxicity.

Keywords Cyanide · Ingestion · Sodium thiosulfate · Antidote · Countermeasure

Introduction

Cyanide is a deadly poison with exposures resulting from accidental or nefarious intention. Several studies and governmental agencies highlight oral cyanide as a potential agent that can be used in a terrorist attack as it can be easily weaponized by contaminating food and water supplies [1–7]. One of the most publicized use of cyanide occurred in 1978 when over 900 people died following ingestion of a beverage laced with cyanide in the "Jonestown Massacre" in Guyana [4]. In 1982

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in Chicago, several people died after taking acetaminophen which was later found to have been laced with cyanide. In January 2019, envelopes reportedly containing potassium cyanide were sent to multiple Japanese companies with letters threatening to lace medications and food with the poison if a large monetary payment to the senders was not made [8]. In 2019, an industrial accident led to the release of cyanide into lake Michigan [9].

Cyanide exposures can occur via inhalation, cutaneous absorption, or ingestion. Compared to other routes of exposure, oral cyanide poses a unique threat [1, 2, 10]. With oral cyanide exposures, patients can have continued absorption after ingestion compared to the inhaled route, where exposures are limited due to cyanide induced apnea [5]. Similar to the signs and symptoms seen with other routes of cyanide exposure, oral exposure to cyanide can be lethal [11]. A primary mechanism of toxicity is via inhibition of cytochrome a3/complex IV of the electron transport chain [3].

Systemically, the enzyme rhodanese transfers sulfur to cyanide to form thiocyanate which is relatively nontoxic [10, 12]. When large exposures to cyanide occur, this mechanism of metabolism gets overwhelmed, leading to cyanide toxicity. Thiosulfate, a Food and Drug Administration (FDA) approved intravenous cyanide antidote, can non-enzymatically react with cyanide to form thiocyanate under certain conditions and also serves as a sulfur donor to rhodanese [10, 12].

Currently, there are no FDA-approved antidotes specific to oral cyanide. Furthermore, the antidotes that are approved are not ideal for use in mass casualty settings since they require intravenous access and have to be administered in large volumes [2]. Also, a large oral exposure can result in a large dose of cyanide that can exceed the capability of conventional antidotes at standard dosing [10]. An oral countermeasure that can neutralize and prevent absorption formation of hydrogen cyanide in the GI tract after oral exposure is needed. Additionally, an oral antidote would provide an alternative treatment that could be used for individuals that have not developed severe toxicity yet are still conscious and can swallow. Having an oral antidote option would allow for conservation of other resources such as intramuscular and intravenous antidotes to be for the severely ill; those who cannot ingest an oral countermeasure at the time of evaluation secondary to severe toxicity.

We hypothesized that thiosulfate given orally would increase survival in swine poisoned by oral cyanide by mitigating the effects of cyanide via mechanisms previously mentioned. Our objective was to evaluate the efficacy of oral sodium thiosulfate on survival and clinical outcomes in a large, swine model of severe cyanide toxicity. In this study, we used our recently developed large, swine model of oral cyanide poisoning that mirrors human toxicity to evaluate the efficacy of oral sodium thiosulfate compared to no treatment [5].

Materials and Methods

Study Design

We conducted a randomized trial comparing oral sodium thiosulfate to no treatment control animals following oral cyanide exposure. 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.

Animal Subjects

Animals (female Yorkshire swine (*Sus scrofa)* weighing 45–55 kg) were randomized using simple randomization into treatment (oral sodium thiosulfate) and control groups. Anesthesia was induced with 10 mg/kg intramuscular ketamine (MWI, Boise, ID) and inhaled isoflurane (MWI, Boise, ID) via nose cone. Animals were intubated with a 7.5–8.0 mm cuffed endotracheal tube, an orogastric tube (B. Braun, Boise, ID) was placed, and peripheral venous access was obtained. Sedation was maintained using the Drager Apollo anesthesia machine (Drager, Houston, TX) with 1–3% isoflurane and 0.4 FiO_2. Tidal volume was set at 8 ml/kg and a respiratory rate 16–20 breaths per minute was used, adjusting the minute volume to maintain an end-tidal CO_2 of 38–42 mmHg. A 7.5 ml/kg bolus of 0.9% saline (B. Braun, Bethlehem, PA) was given via peripheral IV prior to central line placement. Using the M9 ultrasound system, (Mindray, Mahwah, NJ) central venous (external jugular) and arterial (femoral artery) access were obtained. The Drager Infinity Delta Monitor (Drager, Houston, TX) was used to monitor physiologic parameters. After instrumentation, the oxygen was decreased to 0.21 FiO_2, and isoflurane weaned to 0.8–1% until the animal was breathing spontaneously.

Experimental Procedures

Potassium cyanide (8 mg/kg of KCN) (Sigma Aldrich, St. Louis, MO) was diluted in saline (10 mL) and delivered as a one-time bolus dose via the orogastric tube. Three minutes after cyanide administration, those in the treatment group received sodium thiosulfate (510 mg/kg, 3.25 M solution) (Fisher, Fair Lawn, NJ) via orogastric tube (total volume <50 mL).

Doses and timing of countermeasure administration were calculated with guidance from prior studies where those in the treatment group received sodium thiosulfate minutes after exposure to cyanide [13–15]. The dose of sodium thiosulfate was calculated using conversions from a prior study using rabbits [13]. Using the dose that the investigators used in this study, the human equivalent dose was calculated using

equations and the correction factors outlined by Nair et al [16]. The HED value and the correction factor for swine were used to calculate the dose of thiosulfate for this experiment [13, 14, 16]. Cyanide dosing was based on previous studies demonstrating that 8 mg/kg of KCN is lethal in swine [5, 15].

Animals were monitored for 60 minutes or until death, defined as mean arterial pressure (MAP) of less than 30 mmHg for 10 minutes, which we have used as a clinically relevant endpoint in previous large animal studies for cyanide toxicity [5, 14]. Variables including heart rate, oxygen saturation, respiratory rate, body temperature, end-tidal CO_2, and blood pressure were continuously monitored and recorded every 5 minutes.

Outcome Measures

The primary outcome was survival at 60 minutes. Other variables assessed included heart rate, oxygen saturation, respiratory rate, blood pressure, arterial blood gas, serum lactic acid concentration, and blood chemistries.

Euthanasia

Death or 60 minutes after cyanide exposure marked the end of the study. At the end of the study, all animals were euthanized (100 mg/kg sodium pentobarbital IV) in compliance with the Animal Welfare Act and the American Association for Accreditation of Laboratory Animal Care.

Data Analysis

Prism 9.0 (GraphPad, La Jolla, CA) was used for statistical analysis. An anticipated sample size of 5 per group was determined using an alpha of 0.05 and a power of 0.80, estimating an 80% difference in survival between groups.

Values are expressed as median (interquartile range [IQR]). The Mann-Whiteney *U* test was used for for comparison between groups with the 95% confidence interval for the difference between the two medians reported. 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

Analysis of the data after 9 experiments (4 control animals, 5 treatment animals) revealed a statistically significant difference in the primary outcome, survival at 60 minutes. At baseline and time of treatment, physiological parameters including weight, blood lactate, blood pressure, oxygen saturation, and respiratory rate were similar in both groups (Tables 1 and 2). Survival at 60 minutes, the primary outcome, was 0% in the control group compared to 100% in the treatment group (*P*=0.0027) (Fig. 1). Control animals died at 35.0 min (20.2, 48.5) after KCN exposure. Animals in the control group developed apnea by 15 minutes after oral cyanide exposure compared to animals in the sodium thiosulfate treatment group who did not become apneic (Fig. 2a). Animals in the control group developed persistent hypoxia and died while animals in the treatment group transiently developed hypoxia which resolved by the end of the study (Fig. 2b). In the control group, end-tidal CO_2 trended above baseline and by 20 minutes was significantly higher compared to animals treated with thiosulfate (*P*=0.0357). Animals treated with thiosulfate maintained an end-tidal CO_2 near baseline throughout the study (Fig. 2c). Animals in the control group developed hypotension until subsequent death compared to animals treated with sodium thiosulfate which maintained a mean arterial pressure at or near baseline throughout the experiment (Fig. 2d). Blood lactate concentration increased over time in control animals until death, while animals treated with sodium thiosulfate maintained blood lactate levels near baseline until the end of the

Table 1 Physiological parameters at baseline of swine receiving no treatment vs swine treated with thiosulfate.

	Control *n*=4	Thiosulfate *n*=5	95% CI difference	*P* value
Weight (kg)	50.5 (48.4–56.3)	51.0 (50.3–57.6)	−7.4 to 10.5	0.56
Lactate (mmol/L)	0.635 (0.615–0.820)	0.880 (0.740, 1.00)	−0.070 to 0.450	0.079
SBP (mm Hg)	107.5 (104.8–115.5)	114 (107.0–122.0)	−7.0 to 20.0	0.56
MAP (mm Hg)	86.5 (81.3–93.3)	77.0 (81.0–97.0)	−11.0 to 16.0	0.87
Oxygen saturation (%)	93.5 (89.8–97.3)	91.0 (89.5–93.5)	−8.0 to 4.0	0.45
Respiratory rate (breaths per minute)	26.0 (21.25–32.25)	26.0 (20.0–29.5)	−13.0 to 9.0	0.90

There is no significant difference in animal weight, blood lactate, hemodynamics, oxygen saturation, or respiratory rate at baseline

Data are presented as median (IQR)

kg kilogram, *mmol/L* millimole/liter, *mm Hg* millimeters of mercury, *CI* confidence interval

Table 2 Physiological parameters at treatment time of swine receiving no treatment vs swine treated with thiosulfate.

	Control n=4	Thiosulfate n=5	95% CI difference	P value
Lactate (mmol/L)	1.965 (0.093–3.373)	0.760 (0.685–1.050)	−3.09 to 0.25	0.29
SBP (mm Hg)	108 (87.5–120.3)	127.0 (101.0–153.5)	−29.0 to 67.0	0.29
MAP (mm Hg)	76.6 (61.8–93.5)	85.0 (69.0–111.0)	−24.0 to 58.0	0.41
Oxygen saturation (%)	88.5 (73.3–98.5)	89.9 (80.5–94.5)	−24.0 to 20.0	>0.99
Respiratory rate (breaths per minute)	9.5 (2.5–27.8)	14.0 (7.5–22.5)	−23.0 to 25.0	0.73

There is no significant difference in blood lactate, hemodynamics, oxygen saturation, or respiratory rate at the time of treatment

Data are presented as median (IQR)

kg kilogram, *mmol/L* millimole/liter, *mm Hg* millimeters of mercury, *CI* confidence interval

study (Fig. 2e). At the end of the study or death, there was blood lactate concentrations in the treatment group that were significantly lower compared to the control group (P=0.02). There was also a prevention of deterioration in mean arterial pressure in animals treated with sodium thiosulfate compared to the control group (P=0.008), respiratory rate (P=0.02), and oxygen saturation (P=0.02) (Table 3). There were no measurable changes in basic blood chemistries during the 60-minute observation period.

Discussion

In our large animal study of oral cyanide poisoning, we found treatment with oral sodium thiosulfate resulted in 100% survival compared to 0% survival in animals receiving no treatment. We also found clinical outcomes including oxygen saturations, mean arterial pressure, and blood lactate improved with treatment.

In a rabbit model of lethal oral cyanide poisoning, a combination of oral sodium thiosulfate and glycine improved survival [13]. Upon ingestion, it is likely that cyanide is systemically absorbed as hydrogen cyanide (HCN) which is rapidly formed after the cyanide ion is exposed to the acidic pH of the stomach. Thus, we hypothesized the buffering effect of glycine resulted in a shift in equilibrium and thus decreased production of HCN in the stomach, while sodium thiosulfate worked to detoxify cyanide enzymatically via rhodanese [10, 12].

According to the FDA animal rule, for antidotes that cannot be studied in humans, efficacy and safety data must be generated using both small and large animal models. To further assess the efficacy of the combination of oral glycine and oral thiosulfate on the treatment of oral cyanide toxicity, we conducted a study using a large animal model, swine [14]. In that study, animals were poisoned with oral cyanide and randomized into one of two groups, a treatment group that received the combination of oral glycine and oral thiosulfate and a control group that did not receive the treatment. Animals that were treated with the combination all survived until study end while all animals in the control group died.

A more ideal countermeasure, particularly one that can be used in a mass casualty situation, would be a single agent vs a combination of agents as was studied in the rabbit and swine models previously mentioned. This, along with thiosulfate's history of being used in humans for other disease processes is why we chose to explore thiosulfate as monotherapy and build off of a previous study our group conducted using a combination of thiosulfate and glycine for cyanide poisoning[14, 15, 17, 18]. Thiosulfate can enzymatically, via rhodenase detoxify cyanide. Furthermore, thiosulfate has been demonstrated to be safe when administered both orally and intravenously and is currently used therapeutically for other indications [15, 17, 18]. Given these proposed mechanisms and established human administration data, we choose to study the efficacy of oral thiosulfate as a single agent for the treatment of oral cyanide toxicity. In our study, animals treated with oral sodium thiosulfate alone had 100% survival vs 0% survival in the control group in swine poisoned with oral cyanide. This data support that sodium thiosulfate has the potential to serve as a single agent that is efficacious in treating oral cyanide poisoning.

Swine have a similar gastrointestinal and cardiovascular system and are similar in size to humans, allowing for ease of dose scaling [5, 16]. While experiments involving rodents are useful for screening and optimization, hemodynamic monitoring and proper dose scaling of medical countermeasure can be a challenge. Additionally, there are major differences in gastric pH and anatomy between smaller animals and humans [7, 16]. Finally, the Food and Drug Administration (FDA) Animal Rule (2015) suggests data from two species that mimic human toxicity be used for approval of medical countermeasures to chemical toxicants that cannot be studied in humans, like cyanide. A single countermeasure (instead of two drugs administered together) would be easier to administer, particularly if the countermeasure (sodium thiosulfate) has already been demonstrated to be safe when used in humans when administered both intravenously and orally [15, 17, 18].

Table 3 Physiological parameters of swine receiving no treatment vs swine treated with thiosulfate at death or end of study.

	Control *n*=4	Thiosulfate *n*=5	95% CI difference	*P* value
Lactate (mmol/L)	10.250 (5.323–13.120)	0.950 (0.625–2.710)	−13.0 to −2.77	0.02
SBP (mm Hg)	43.0 (33.3–48.3)	106.0 (101.0–108.0)	52.0–75.0	0.02
MAP (mm Hg)	24.5 (18.8–28.0)	80.0 (76.0–86.5)	48.0–69.0	0.008
Oxygen saturation (%)	38.0 (18.0–64.8)	89.0 (87.0–91.0)	19.0–73.0	0.02
Respiratory rate (breaths per minute)	0 (0–0)	24.0 (23.5–28.0)	23.0–29.0	0.02

There was a significant difference in blood lactate, hemodynamics, oxygen saturation, and respiratory rate at the time of death or end of study

Data are presented as median (IQR)

kg kilogram, *mmol/L* millimole/liter, *mm Hg* millimeters of mercury, *CI* confidence interval

In a mass casualty event, triaging victims is of extreme importance. An oral antidote that could be self-administered would allow health care providers to direct other resources to patients who are more critically ill. With ingestion, a large amount of cyanide can accumulate in the stomach before absorption and the development of severe illness, which may necessitate large doses of antidote that cannot be tolerated via intravenous or intramuscular administration [10]. In situations like this, an oral antidote would be ideal.

Future studies will be aimed at dose optimization, delaying the time to treat, and determining if combining oral and intramuscular administration of sodium thiosulfate increases efficacy following mass ingestions of cyanide.

Limitations

Our study has limitations. This was an animal study and there are differences between swine and humans. However, swine are similar in anatomy and size to humans. Additionally, swine have similar gastrointestinal and cardiovascular physiology when compared to humans, making swine an excellent choice for an animal model of human cyanide toxicity [5, 14]. We used anesthesia in our model which may have effects on the toxicity and efficacy of the agents administered in the study. However, both treatment and control animals received similar doses of anesthetic and the use of anesthesia was required by our IACUC. Furthermore, the oral sodium thiosulfate was administered 3 minutes after cyanide exposure. In severe toxicity, victims may rapidly lose consciousness and develop apnea, rendering them incapable of ingesting an oral antidote within that time frame. Exploring the efficacy of thiosulfate later after exposure to cyanide would be of interest. Additionally, our power calculation revealed that 5 animals per group was the targeted number of experiments. The data presented is from 9 animals, and it is possible that the tenth data point could have changed the statistical calculations. Our group had run an interim analysis after the ninth experiment and detected a statistical difference. The staff conducting the experiments were also responsible for mixing the reagents for treatment and exposure. As a result, they were not blinded to the intervention; however, there

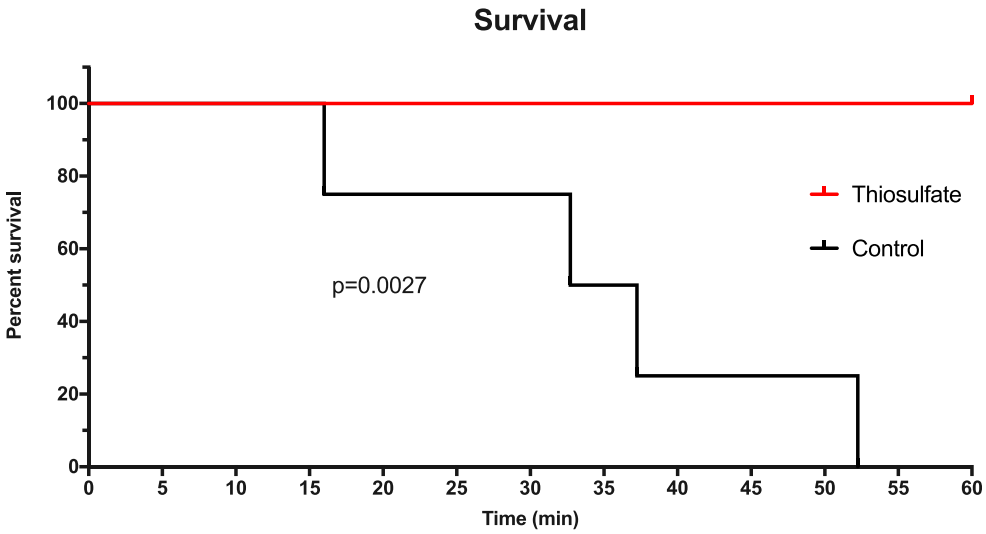

Fig. 1 Percent survival in swine treated with oral sodium thiosulfate compared to controls. Survival is improved with oral sodium thiosulfate administration following oral cyanide exposure compared to controls. *P* value determined by log-rank (Mantel-Cox) test for comparison, *P* value ≤ to 0.05 is considered significant.

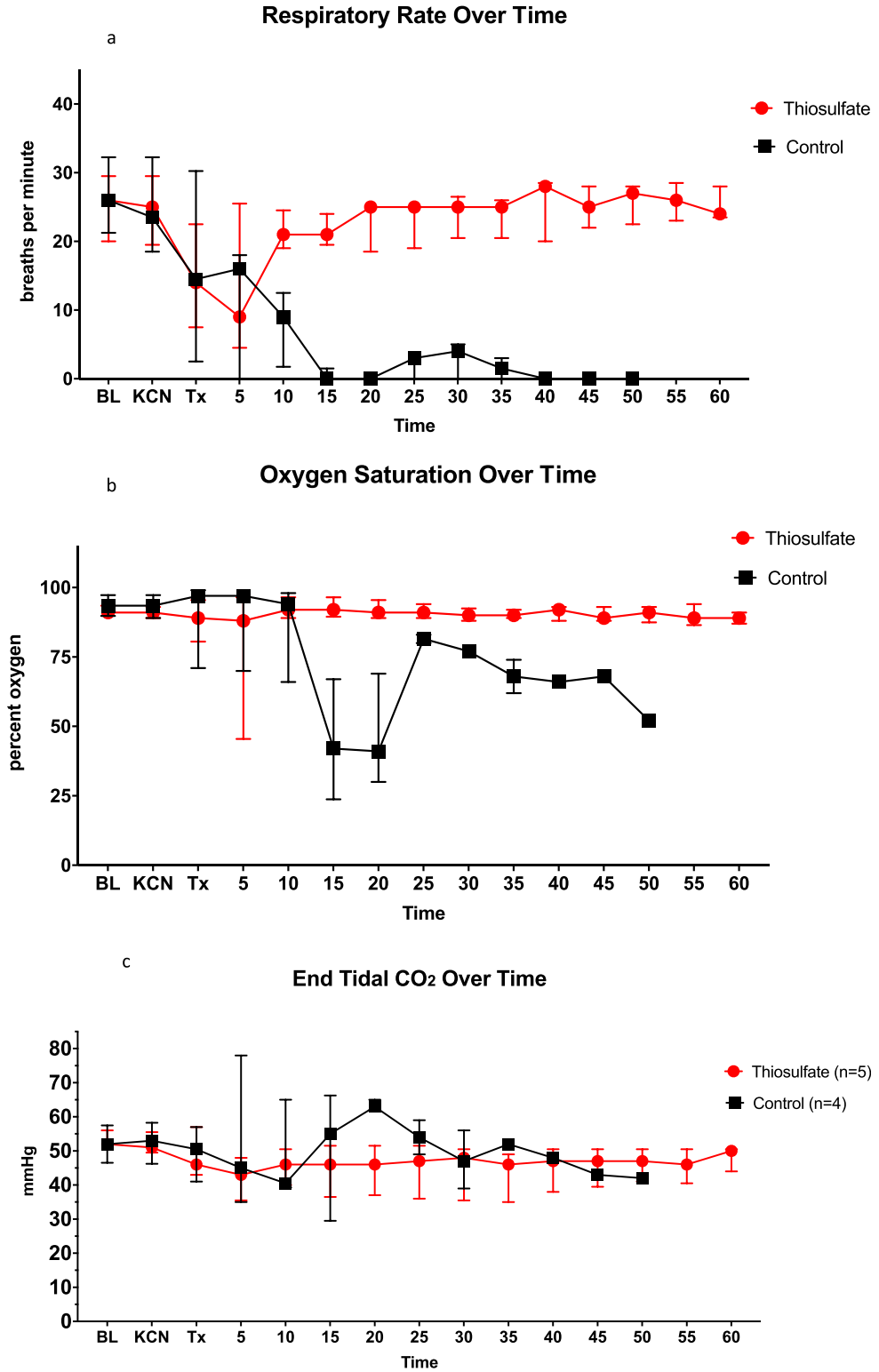

Fig. 2 Physiological parameters and blood lactate over time (min) in animals treated with sodium thiosulfate compared to controls. BL: baseline; TX: treatment with oral thiosulfate. **a**–**e** Physiological parameters and blood lactate over time (minutes) between animals treated with sodium thiosulfate and controls. **a** Animals in the control group developed apnea compared to animals in the sodium thiosulfate treatment group. **b** Following oral cyanide exposure treatment animals had a decrease in oxygen saturation which returned to baseline by the end of the study. **c** Animals in the control group had a slight increase in end-tidal CO_2 which decreased over time. **d** The sodium thiosulfate treatment group maintained mean arterial blood pressure throughout the experiment compared to controls. **e** Blood lactate increased over time in control animals until death while animals in the sodium thiosulfate group maintained blood lactate levels near baseline until the end of the study. Data are presented as median (IQR). mmol/L: millimoles/liter; mg/dL: milligrams/deciliter; BL: baseline; Tx: treatment with oral thiosulfate.

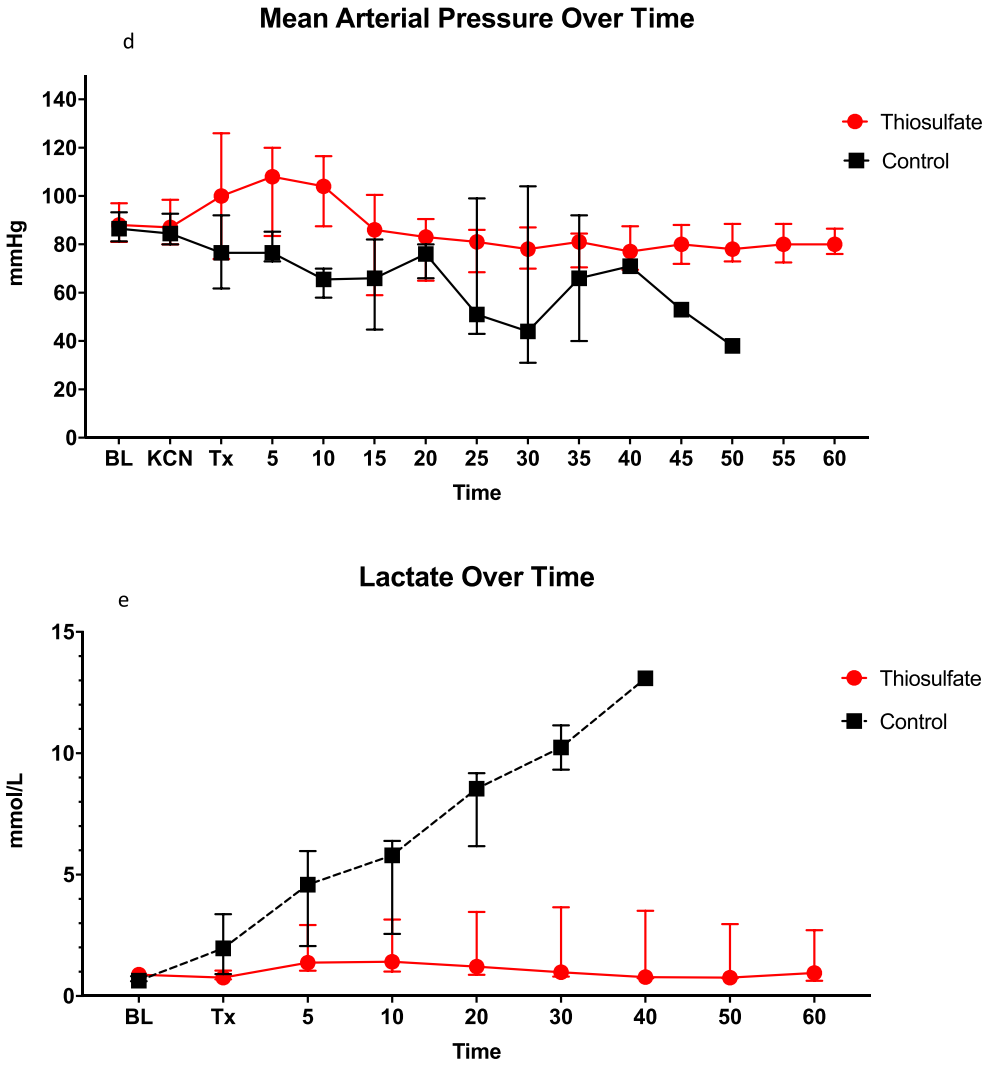

Fig. 2 continued.

was a significant difference in survival between the two groups.

Conclusion

Oral administration of sodium thiosulfate alone improved survival, blood pressure, respiration, and blood lactate concentrations in a large animal model of acute oral cyanide toxicity. Future studies exploring the efficacy of sodium thiosulfate administered later in the clinical course are warranted to further assess its potential application as an antidote for cyanide exposure.

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Declarations

Conflicts of interests The authors have no conflicts of interest to disclose.

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