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13. SUPPLEMENTARY NOTES						
14. ABSTRACT Objective: To compare the return to baseline of mean arterial blood pressure (MAP) between 3 groups of swine with acute CN toxicity and treated with HOCOB, ST, or a combination of HOCOB+ST. 36 swine (48-52kg) were intubated, anesthetized, instrumented and then poisoned with a continuous CN infusion, until the development of severe hypotension (Time 0-50% of baseline MAP). Animals were randomly assigned to the groups and monitored for 60 min after the start of the antidotal infusion. Baseline mean weights, time to hypotension, and CN dose at hypotension were similar. Mean CN blood levels and lactate levels at Time 0 were also similar. All of the 12 animals in the ST group died before the conclusion of the study as compared to 2 in the HOCOB/ST group and 1 in the HOCOB group. Conclusion: Sodium Thiosulfate failed to reverse cyanide-induced shock in our swine model of severe cyanide toxicity. ST also failed to augment the efficacy of HOCOB on cyanide-induced shock in our model of severe cyanide toxicity. HOCOB was again found to be effective in treating severe cyanide toxicity.						
15. SUBJECT TERMS Cyanide, cardiac arrest, hydroxocobalamin, sodium thiosulfate						
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WHMC – Animal Final Report

1Aug2011

1. Protocol Number: FWH20090023A

2. Type of Research:
Animal Research

3. Title:

Sodium thiosulfate versus hydroxocobalamin in the treatment of acute, severe cyanide induced cardiotoxicity in a swine (Sus Scrofa) model

4. Principal Investigator (PI):

Name	Rank	Date of IACUC Training	Branch of Service/ Corps	Staff Resident Fellow Civilian	Department / Office Symbol	Email (if other than WHMC Outlook)	Phone	Pager
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5. Purpose:

Cyanide is industrial chemical that has been used for terrorism. It is also a common agent used for suicide and causes lethal manufacturing site accidents. It is rapidly lethal and commonly produces low blood pressure, sedation, and acid in the blood. Half of patients who are intoxicated by cyanide develop cardiac arrest or severely low blood pressure. Currently several antidotes exist, but many have severe adverse effects. Of these, two agents have few adverse effects and have been used to treat cyanide toxicity – sodium thiosulfate (ST) and hydroxocobalamin. Hydroxocobalamin is available in the US as of 2007, but is 400 times the cost of sodium thiosulfate. Hydroxocobalamin has never been compared with sodium thiosulfate in a hypotensive model. **The purpose of our study is to directly compare two antidotes in a swine model of cyanide-induced toxicity, manifested by low blood pressure.** If the two treatments are equal in effectiveness, then the treatment of acute cyanide toxicity in the US will be changed – sodium thiosulfate would be considered as a first line single agent for cyanide toxicity

Fifty-three animals were anesthetized and placed on a breathing machine. They were intoxicated with cyanide (infused through the vein) until the blood pressure was low. The animals were assigned to one of three treatment groups. The treatment was infused through the vein. We collected blood samples and vital signs measuring the effect of each treatment. **We measured nitric oxide levels, which if abnormal, would lead to breakthrough in the understanding of cyanide toxicity and antidotal treatments.** At the end of the 50-minute experiment, we euthanized the animals.

Hypothesis

We hypothesize that there will be no difference between the return to baseline of mean arterial blood pressure between the three treatment groups (hydroxocobalamin versus sodium thiosulfate versus combination of antidotes).

To test this hypothesis we will test the following research question:

- 1) Is there a statistically significant difference in the rate of return to baseline of mean arterial blood pressure between the three groups as measured by repeated measures analysis of variance and/or Cox proportional hazards model?
- 2) Is there a difference in the proportion of pigs surviving at the end of the experiment?

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- 3) Is nitric oxide elevated during cyanide-induced hypotension and do the antidotes reduce the serum nitric oxide?
- 4) **The study will be a GME tool to advance the education of a resident (Capt Tuepker). I will teach the resident the fundamentals of research, toxicology, and resuscitative science. It will fulfill his GME research requirement and allow him opportunity for scientific presentation and publication.**

6. Results:

We were successful in consistently inducing cardiotoxicity in all study animals. Our lab values are consistent with cyanide toxicity. At this point hydroxocobalamin alone or in combination with sodium thiosulfate has yielded a more positive result, as evidenced by reverse of hypotension, and resolve of other cyanide induced effects in the majority of the animals. We temporarily halted data collection to look into possible causes of this problem, and worked with Merck Sante, King Pharmaceuticals and Meridian Medical Technologies to help tease out the issue. We modified our methods slightly to a less severe model and have successfully completed data collection. Our own evaluation of the hydroxocobalamin from the different suppliers showed no difference in the area under the curve. As expected, all sodium thiosulfate pigs have died within the first 5 minutes after hypotension.

Data analysis is complete and abstract is included in this report. We have completed the manuscript, and thus plan to create the DTIC report in July 2011. We presented to SAEM and won Best Basic Science Award at the national meeting, competing against 1,100 other abstracts with our oral plenary presentation. We plan to submit the manuscript to Annals of Emergency Medicine and will acquire proper CRD and 59th MDW approval.

7. How may your findings benefit the Air Force?

This study provides support for hydroxocobalamin alone for cyanide toxicity. Recently the US Army was weighing whether to support the sodium thiosulfate alone or hydroxocobalamin in a combat setting. Our study answers that question for critically ill cyanide toxic animals. Our findings will also benefit DoD providers who treat cyanide toxicity from chemical exposures or structural fires.

8. Number of Animals

Projected Enrollment of Animals at the Beginning of Study:
36 experiment animals, 1 protocol development animal

Amendment #1 Dated 29Dec2009 requested 12 additional animals and 4 animals were repeated.

Actual Number of Animals Enrolled: 37 that were originally approved, 12 per amendment #1, and 4 repeated animals (replaced by Dr. Harroff without an amendment) for a total of 53.

9. Status of Animals Entered Into the Protocol:

All animals were in good health.

10. Status of Funds:

All funds have been allocated.

11. Reason for Closure:

- Objectives of the study were met

12. Specific Problems:

- 1) There was an unexpected shortage of hydroxocobalamin in the United States. This set us back by 4 months.

13. Publications and Presentations:

Presentations:

- 1) GSACEP Joint Services Symposium-poster, April 2010- Preliminary data was presented
- 2) AFMS-August 2010-presentation
- 3) ACEP-September 2010-poster
- 4) SAEM-June 2010 oral-final data
- 5) AFMS-August 2011-poster with final data

These Presentations and Publications have been cleared by 59 CRD and Public Affairs.

Publications:

None

These Presentations and Publications have been cleared by 59 CRD and Public Affairs.

14. Exceptional Achievements:

We presented to SAEM and won Best Basic Science Award at the national meeting, competing against 1,100 other abstracts with our oral plenary presentation.

15. Signature of Principal Investigator:

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