

REPORT DOCUMENTATION PAGE

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6. AUTHOR(S) Varney, Shawn Bebarta, Vikhyat Pearce, Brett Boudreau, Susan Vargas, Toni Castaneda, Maria				8. PERFORMING ORGANIZATION REPORT NUMBER FWH20100054A	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) 59th EMS Wilford Hall Ambulatory Surgical Center 2200 Bergquist Drive Lackland AFB, TX 78236				10. SPONSOR/MONITOR'S ACRONYM(S)	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Office of the Air Force Surgeon General Directorate for Modernization, SGRS 5201 Leesburg Pike, Suite 1206 Falls Church, VA 22401				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Distribution A. Approved for public release; distribution unlimited.					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Obj:Compare IV fat emulsion(IFE) and sodium bicarbonate(SB) in critically ill diphenhydramine(DPH) swine to determine which better improves hypotension(hypo). Method:Swine 45-55kg infused with DPH 1mg/kg/min IV until MAP fell to 60% of baseline (BL), randomized to IFE or SB. Measured HR, SBP, MAP, CO, SVR, & SvO2. Labs for pH, pCO2, bicarb, lactate, & DPH level. DPH level found by liquid chromatography. Results:24 swine, 12 each to IFE & SB group. At BL, vital signs similar in each group. IFE & SB group had similar amt of DPH to hypo(IFE: 31.21mg/kg; SB: 33.28mg/kg). IFE to hypo at mean 32:13min; SB at 34:08min. Post hypo, no difference in IFE & SB groups for CO, SVR, SvO2, QRS, or QTc; though, better HR in SB, SBP in IFE, & MAP in IFE. IFE group died at mean 12:33min; SB at 07:48min. One IFE and two SB pigs survived. Mean total serum DPH levels end of study similar. Mean DPH in lipid layer was 6.8mcg/mL, in aqueous layer 8.6mcg/mL. Conc:No difference in hypo between IFE & SB. IFE didn't improve QRS widening in DPH toxic swine. DPH level similar in aqueous & lipid layers.					
15. SUBJECT TERMS Diphenhydramine, Intralipid, sodium bicarbonate, intravenous fat emulsion, poisoning, overdose, toxicity, and antidote					
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WHASC – Animal Final Report

13 Nov 2012

1. Protocol Number: FWH20100054A

2. Type of Research:

Animal Research

3. Title: "Intravenous fat emulsion therapy versus sodium bicarbonate effect on hypotension and QRS measurement in a swine model (*Sus scrofa*) of diphenhydramine toxicity"

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 WHASC Outlook)	Phone	Pager
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5. Purpose:

This study will replicate 2 well designed studies in smaller animals that a known lipophilic drug responded favorably to IFE, and that animals respond as anticipated to known, standard therapies (bicarbonate).

6. Results: The basic finding was that intravenous fat emulsion (IFE) did not perform better than the standard antidote (sodium bicarbonate - SB) in an amitriptyline-induced cardiotoxic swine model. IFE did not improve hypotension or QRS widening compared to SB.

Specifically, we found the following: There was no difference at baseline for each group in any hemodynamic parameter or electrocardiogram interval - mean heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), cardiac output (CO), and QRS interval. Both groups required similar diphenhydramine doses and similar times to reach hypotension. After hypotension there was no difference between groups for CO, but HR was lower with SB ($p < .008$), and SBP and MAP were transiently higher with IFE ($p < .003$, $p < .005$ respectively). There was no difference in QRS or QTc intervals after hypotension or at the end of the study. Animals in both groups died at similar times. One IFE and 2 SB pigs survived. IFE aqueous layer contained 54.5% of total measurable diphenhydramine, while the fatty layer contained 42.9%.

Conclusion: In our diphenhydramine-induced hypotensive swine model, we did not detect a difference in hypotension mitigation between IFE and SB. IFE did not improve QRS widening. Similar amounts of DPH were in the aqueous and lipid layers.

7. How may your findings benefit the Air Force? These findings support not using IFE for diphenhydramine-induced hypotension. There was no difference between IFE and SB. Bicarbonate is inexpensive, has a long shelf life, and is readily available. IFE did not improve hypotension and should not be pursued as an antidote for lipophilic agents in overdose.

8. Number of Animals

Projected Enrollment of Animals at the Beginning of Study: 28
Actual Number of Animals Enrolled: 43

Amendments: Amendment #1 Dated 31Jan2011-10 animals, Amendment #2 Dated 19Apr2011-5 animals

9. Status of Animals Entered Into the Protocol:

All animals were in good general health and were euthanized per protocol.

10. Status of Funds:

All funds were executed.

11. Reason for Closure: Objectives of the study were met.

12. Specific Problems:

During the protocol development phase we were able to create a lethal model for diphenhydramine toxicity. However, all the animals died after they reached cardiotoxicity from the diphenhydramine infusion even when treated with the IV fat emulsion antidote. Given the antidote's apparent lack of efficacy, we stopped the experiment early and studied only a total of 10 experimental animals. Unfortunately, we were not aware of the need for an apparent larger-than-usual number of animals required to achieve sufficient statistical power to show a definitive lack of efficacy of the new antidote at the dose of 1.5 mL/kg. Therefore, we amended the study to include 10 animals: 1) four to be used to evaluate swine response to IFE therapy in cardiotoxicity from a lipophilic drug (Verapamil); and 2) six swine to be evaluated for treatment of nortriptyline toxicity (a TCA) and treatment with standard therapy (sodium bicarbonate). Statistical analysis will then occur in the months following data collection.

We have completed the first portion of the amendment using IFE for verapamil toxicity in four swine. The numbers are very small since this was simply a feasibility study to show that IFE for verapamil in swine acted the same as in dogs. We did not continue with the second arm of the first amendment reasoning that it would not change our experiment. We chose to move on to the next stage.

We wrote a second amendment to this study asking for 5 additional animals to the originally requested 28 (24 animals total) to give acceptable power to the statistical analysis and have proceeded with a "negative" study model in the second amendment.

We have completed conducting this final phase of the DPH experiment. Data collection was completed by August 2011.

13. Publications and Presentations:

Presentations:

Poster presentation at American College of Medical Toxicology meeting, Clearwater Beach, FL, March 2011

Poster presentation at MHSRS/ATACCC, Ft. Lauderdale, FL, August 2012.

Moderated electronic poster at American College of Emergency Physicians Scientific Assembly, Denver, CO, October 2012

Publications:

None. Manuscript preparation in progress.

14. Exceptional Achievements:

None

15. Signature of Principal Investigator:



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