Comparison of Resuscitation Protocols Using Lipid Emulsion for Bupropion Overdose in a Swine Model

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Conflict of Interest Disclosure Statement

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The investigators of this research have no financial relationships with any commercial interest related to the content of this activity.

No off-label uses will be discussed during this presentation.
Significance

- 1 in 5 Combat Veterans suffers from PTSD
- Wellbutrin commonly prescribed for depression, alcohol abuse, smoking cessation and post traumatic stress syndrome (PTSD)
- #s on Suicide = risk of intentional overdose
Wellbutrin

- Highly lipophilic atypical antidepressant

- In 2012, one fifth (~21%) of antidepressant overdose fatalities were from Wellbutrin

- Toxic plasma concentrations cause cardiac toxicity that almost always results in death
Problem Statement

No studies have determined the optimal combination of lipid rescue and traditional ACLS therapy for treatment of Wellbutrin overdose.
Research Questions

- Is there a difference in survival between the resuscitation groups?
- Is there a difference in time to return of spontaneous circulation (ROSC) between resuscitation groups?

Theoretical Framework

- Pharmacodynamics of Wellbutrin
- ACLS Guidelines
- Lipid Sink Theory
Literature Review

Pretreatment or Resuscitation with a Lipid Infusion Shifts the Dose–Response to Bupivacaine-induced Asystole in Rats

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Animal studies show efficacy of intravenous lipid emulsion in the treatment of severe cardiotoxicity associated with local anesthetics, clonidine, and verapamil, possibly by trapping such lipophilic drugs in an expanded plasma lipid compartment ("lipid sink"). Recent case reports describe lipid infusion for the successful treatment of refractory cardiac arrest caused by perinatal administration of local anesthetics, but clinical evidence has been lacking for lipid’s antiarrhythmic efficacy in toxicity caused by ingested medications. A 5.5-year-old girl developed severe respiratory and cardiovascular collapse after intentional ingestion of up to 7.35 g of bupropion and 4 g of lamotrigine. Standard cardiopulmonary resuscitation for 70 minutes was unsuccessful in restoring sustained circulation. A 100-Hz, intravenous bolus of 50 mg lipid emulsion was then administered, and after 1 minute an effective sustained pulse was observed. The patient subsequently manifested significant acute lung injury but had rapid recovery. Intravenous lipid emulsion is a promising treatment for cardiotoxicity from bupropion and lamotrigine. Our case report of a patient with toxic ingestions and unresponsive cardiac arrest within 30 minutes of bupropion levels before and after lipid infusion parallels triglyceride levels. This patient developed carboxylic acidosis because of metformin, oral overdose of bupropion and lamotrigine that was initially refractory to standard resuscitation measures. An infusion of lipid emulsion was followed rapidly by restoration of effective circulation. Toxicologic studies are consistent with the lipid sink theory of antiarrhythmic efficacy. [Ann Emerg Med. 2008;52:412–416.]
Combined Lipid Emulsion and ACLS Resuscitation Following Bupivacaine- and Hypoxia-Induced Cardiovascular Collapse in Unanesthetized Swine

This study examined whether combining lipid emulsion and advanced cardiac life support (ACLS) improves survival in an unanesthetized swine model of bupivacaine- and hypoxia-induced cardiovascular collapse. Arterial and venous catheters and a tracheotome were surgically placed in 28 swine receiving inhalation anesthetics. After a 1-hour recovery period, bupivacaine (5 mg/kg) was administered intravenously over 15 seconds. Following 1 minute of observation and 3 minutes of mechanical airway obstruction, during which all animals exhibited complete cardiovascular collapse, ACLS was initiated. Animals were randomized to receive either 10% saline or 20% lipid emulsion commencing with 10 ml/kg of fluid administered over 1 minute. ACLS was continued for 30 minutes after the 10 ml/kg initial dose. The combination of lipid emulsion and ACLS did not improve survival from bupivacaine- and hypoxia-induced cardiovascular collapse in unanesthetized swine.

Literature Review

Comparing Resuscitative Measures for Bupivacaine Toxicity Utilizing Lipid Emulsions in a swine model (Sus scrofa)

Abstract

Introduction: A toxic dose of bupivacaine causes cardiac arrhythmias and ultimately asystole. Resuscitation is difficult and almost always unsuccessful. Until recently, cardiopulmonary bypass was the only effective treatment. Anecdotal evidence suggests that infusion of lipid emulsion may be an effective treatment. No studies have determined the optimal combination of lipid rescue and traditional Advanced Cardiac Life Support (ACLS) therapy for a toxic dose of bupivacaine. The purpose was to determine the optimal combination of lipid rescue and traditional ACLS therapy for treatment overdose of bupivacaine.
Research Design

“Prospective, randomized, between subjects experimental design”

Eight treatment groups:

1. CPR
2. Lipid only
3. Vasopressin
4. Epinephrine
5. Vasopressin + Lipid
6. Epinephrine + Lipid
7. Epinephrine + Vasopressin
8. Epinephrine + Vasopressin + Lipid

Data Collection Procedures

Wellbutrin Overdose (35 mg/kg)  Pulse?  CPR  Treatment Protocol  Assessment (Every 2 min)  ROSC?  30 Min
Instruments

- Thumper
- Vigileo

Statistical Analysis

- MANOVA on pretest data
- Survival Analysis
- Odds Ratio
- Chi Square
### Results

**Return of Spontaneous Circulation (ROSC)**

![Graph showing the percentage of ROSC for different treatments.](image)

**Minutes to Return of Spontaneous Circulation (ROSC)**

![Graph showing the minutes to ROSC for different treatments.](image)
Results

![Graph showing ROSC percentages for EPI Groups Combined and All other groups.]

Conclusion

- **Limitations**
  - Swine
  - Add

- **Implications**
  - Lipid Emulsion for Wellbutrin overdose
  - Lipids plus Epinephrine may be best practice

- More research is needed
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• Washington Association of Nurse Anesthetists

Questions?
Literature Review


Power Analysis

• Alpha- 0.05
• Power- 0.80
• 7 swine were needed for each of the 8 groups
Operational Definitions

- Toxic dose
  - Dose to create a non-perfusing arrhythmia
- Return to spontaneous circulation (ROSC)
  - Unassisted pulse with systolic arterial blood pressure > 60 mmHg for minimum of 10 minutes
- Non-perfusing arrhythmia
  - Arrhythmia that results in 10% or less of baseline (normal) cardiac output
- Normal cardiac output
  - 3-7 liters per minute
- Standard ACLS drug therapy
  - Current protocols described in the American Heart Association
  - Instructor manual dated 2010

Swine Information

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