

Intravenous Lipid Emulsion: The Gift of the Glob

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Conflict of Interest Disclosure

- ▶ I do not have any conflicts of interest to disclose
- ▶ Intralipid® is manufactured by Baxter
- ▶ Liposyn® is manufactured by Hospira
- ▶ I do not have any financial ties with any manufacturers or promoters of this product

Objectives

- ▶ Make clinical decisions based on the theoretical benefits of IV lipid emulsion therapy for life-threatening poisonings
- ▶ Treat patients based on the potential role of IV lipid emulsion therapy in specific toxicological scenarios
- ▶ Administer IV lipid emulsion therapy at an appropriate dose

What is Intralipid®?

- ▶ Intravenous Lipid or Fat Emulsion (IFE)
- ▶ 20% Soybean Oil or Safflower Oil, 1.2% Egg Yolk Phospholipids, 2.25% Glycerin, and Water for Injection
- ▶ Rich in essential polyunsaturated fatty acids: linolenate and linoleate



Traditional Uses of IFE

- ▶ TPN
- ▶ Delivery vehicle for highly lipid soluble drugs:
 - Propofol
 - Paclitaxel
 - Etomidate
 - Diazepam
 - Amphotericin

Collins-Gold et al. Advanced Drug Delivery Systems Review. 1990. 5:189-208

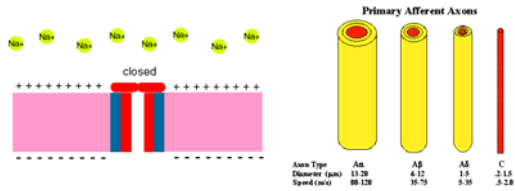
Discovery of IFE as Antidote

- ▶ Carnitine deficiency thought to be a risk factor for arrhythmias after bupivacaine use
 - Carnitine shuttles FA into mitochondria
 - Fatty acids accumulate in cytosol without carnitine
 - Pre-treatment with IFE should make it worse!
- ▶ The opposite was seen in animal studies
 - IFE made carnitine deficient rats more resistant to bupivacaine-induced asystole

Weinberg. J Clin Anesth. Dec 1997;9:668-70.

Local Anesthetic Action

- Blocks nerve conduction by interaction with voltage gated sodium channels



Local Anesthetic Dosage for Infiltration

- Lidocaine
 - Should not exceed 4.5 mg/kg
 - Or 7 mg/kg with epinephrine
- Procaine
 - Should not exceed 8 mg/kg
 - Or 10 mg/kg with epinephrine
- Bupivacaine
 - Should not exceed 2.5 mg/kg
 - OR 3 mg/kg with epinephrine

Local Anesthetic Toxicity

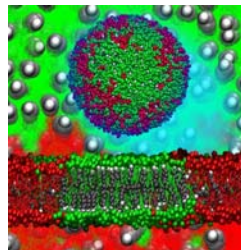
- Neurotoxicity
 - Precedes cardiotoxicity
 - Lightheadedness, tremors, peri-oral numbness, anxiety, euphoria
 - Seizures and Coma
- Cardiotoxicity
 - Hypotension, bradycardia, asystole
 - Sinus bradycardia, AV block, increased PR and QRS intervals, VT/VF, asystole

Local Anesthetics

- Potency and duration of action increases with lipid solubility:
 - Tetracaine > bupivacaine > etidocaine > lidocaine > mepivacaine > prilocaine > procaine
- Risk of neurotoxicity and cardiotoxicity:
 - Bupivacaine** > etidocaine > lidocaine > mepivacaine > prilocaine

Mechanism of Action of IFE: Lipid Sink Theory

- Lipid sink theory
 - Intravenous reservoir that binds excess drug
 - Eventually drug is still released but prolongs time needed for metabolism



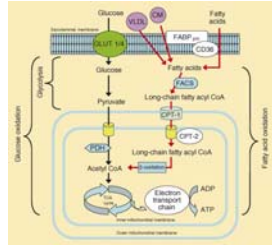
Mechanism of Action of IFE: Lipid Sink Theory

- Animal studies shows greater efficacy after experimental overdoses of more lipid soluble drugs
 - Octanol/water partition coefficient (log P)
 - Propranolol (3.5)
 - Verapamil (3.8)
 - Clomipramine (5.2)
 - Bupivacaine (346)



Mechanism of Action of IFE: Increase Myocardial Fuel

- ▶ Resting myocardium
 - Preferred substrate is FA (up to 90%)
 - Remainder from glucose oxidation
- ▶ Stressed myocardium
 - Glucose becomes preferred substrate
- ▶ IFE enhances any contribution from FA oxidation during stress state



Literature Evidence: Animal Studies

- ▶ Animal studies showing efficacy with experimental OD models:
 - Local Anesthetics (bupivacaine)
 - Calcium Channel Blockers (verapamil)
 - Beta Blockers (propranolol)
 - TCAs (clomipramine)
- ▶ One study comparing hyperinsulinemia euglycemia therapy in verapamil OD showed same outcome

Animal Studies Evidence

Lipid Emulsion Infusion Rescues Dogs From Bupivacaine-Induced Cardiac Toxicity

Guy Weinberg, M.D., Richard Ripper, B.A., Douglas L. Feinstein, Ph.D., and
Methods: Bupivacaine, 10 mg/kg, was administered intravenously over 10 seconds to fasted dogs under isoflurane general anesthesia. Resuscitation included 10 minutes of internal cardiac massage followed with either saline or 20% lipid infusion, administered as a 4-mL/kg bolus followed by continuous infusion at 0.5 mL/kg/min for 10 minutes. Electrocardiogram (EKG), arterial blood pressure (BP), and myocardial pH (pHm) and pO₂ (pmO₂) were continuously measured.

Results: Survival after 10 minutes of unsuccessful cardiac massage was successful for all lipid-treated dogs (n = 6), but with no survivors in the saline controls (n = 6) (P < .01). Hemodynamics, PmO₂, and pHm were improved during resuscitation with lipid compared with saline treatment in which dogs did not recover.

NS 0/6 vs. IFE 6/6 survived

Weinberg G. Reg Anesth Pain Med May 2003; 29: 198-202

Hemodynamic Effects of Intravenous Fat Emulsion in an Animal Model of Severe Verapamil Toxicity Resuscitated with Atropine, Calcium, and Saline

Theodore C. Bania, MD, MS, Jason Chu, MD, Eric Perez, MD, Mark Su, MD, In-Hei Hahn, MD

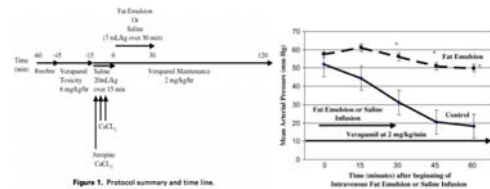


Figure 1. Protocol summary and time line.

NS 1/7 vs. IFE 7/7 survived

Acad Emerg Med. Feb 2007;14:105-11

Literature Evidence: Humans

- ▶ No IFE clinical trials have been done!
- ▶ Local Anesthetics: 39 case reports of successful therapy after cardiac arrest
- ▶ Other Substances:
 - Calcium Channel Blockers
 - Beta Blockers
 - TCAs
 - Atypical antidepressants
 - Antipsychotics

Human Evidence: Case Reports

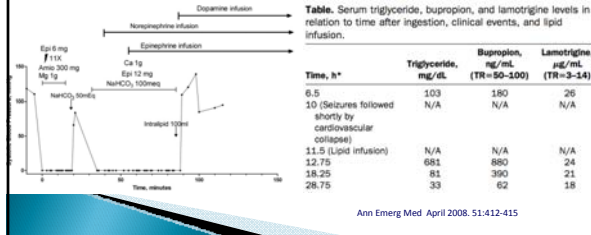
- ▶ Patient receives axillary nerve block for hand surgery in OR.
- ▶ After administration of local anesthetic develops confusion, slurred speech, twitching, tachycardia with frequent PVCs
- ▶ IFE 20% given immediately, with no other interventions
- ▶ Speech cleared within 1 min, twitching within 3 min, HR back to baseline and no PVCs after 6 min

Jamaty. Clinical Toxicology. 2010 Jan. 48, 1-27

Use of Lipid Emulsion in the Resuscitation of a Patient With Prolonged Cardiovascular Collapse After Overdose of Bupropion and Lamotrigine

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IFE Dosing Regimen

- ▶ Intralipid® or IFE 20%
 - Start 1.5 mL/kg IV bolus (lean body mass)
 - Then 0.25 mL/kg/minute infusion, may double the dose for persistent hypotension
 - May repeat bolus 1-2 times for persistent asystole
 - Maximum recommended dose is 10 mL/kg during initial 30 minutes

www.lipidrescue.org

Potential Adverse Effects

- ▶ Anaphylaxis
 - Allergy to ingredients is an absolute contraindication: eggs, soy, safflower
- ▶ Fat emboli/Acute Lung Injury
 - Not seen in animal models at higher doses
- ▶ Extrapolated from TPN
 - Fat emboli seen in premies with high TPN doses
 - Increased susceptibility to infection
 - Thrombophlebitis

Potential Adverse Effects: Drug Binding

- ▶ Potential for binding to therapeutic lipid soluble drugs
 - ? Amiodarone (log P=7.8)
- ▶ Human case reports and animal studies show no interaction with:
 - Atropine
 - Calcium
 - Bicarbonate
 - Insulin
 - Glucagon
 - Flumazenil

Known Adverse Effect

- ▶ Lipemia interferes with laboratory analysis
 - CBC
 - CMP
 - ABG



West et al. Clin Toxicol. May 2010; 48(4):393-6.

So, is IFE safe?

AAGBI Safety Guideline

Management of Severe Local Anesthetic Toxicity

ACCOMPANYING NOTES

- 1 Recognition**

Local anesthetic intoxication can present in many different ways, making it very difficult to recognize. After injection of a bolus of local anesthetic, toxicity may develop at any time in the following hour. Techniques involving infusion of local anesthetics through a catheter allow optimization for dosing at any time.
- 2 Immediate management**

Some hospital laboratories have encountered difficulty analyzing blood drawn during lipid emulsion therapy. If clinical circumstances allow, it may be prudent to draw blood for later analysis before lipid emulsion therapy begins.
- 3 Treatment**

100 mL of 20% lipid emulsion should be immediately available to all patients receiving potentially cardiotoxic doses of local anesthetics. 20% lipid emulsion is readily available from most hospital pharmacies, which may also be able to help departments with timely replacement of high-molarity sodium bicarbonate. 20% emulsion has been used in the majority of reported cases of lipid emulsion as an antidote. Alternative preparations have also been used in successful resuscitations. Although some preservative preparations are provided in Intralipid®, e.g., Bupivacaine®, there are not a suitable alternative due to the significant cardiotoxicity depression caused by the preservative. This does not preclude the use of small, incremental doses of preservative lipid emulsions. In extremely obese patients, doses of lipid emulsion should ideally be based on an estimate of lean body weight. The interaction between lipid emulsion treatment and other cardiovascular drugs used in resuscitation is unclear. Some evidence suggests high doses of vasopressors are harmful to resuscitation in local anesthetic intoxication. Conversely, some evidence suggests lipid emulsion therapy may be harmful in peripheral cardiac arrest.

Scenarios

- ▶ **Scenario 1:**
- ▶ Patient develops life-threatening hemodynamic or neurological deterioration after administration of local anesthetic
- ▶ Risk-Benefit analysis:
 - Beneficial: Numerous case reports in the literature. Increasing support by anesthesiologists.

Scenarios

- ▶ **Scenario 2:**
- ▶ Patient develops life-threatening hemodynamic compromise after lipid soluble drug OD (CCB, beta blockers, antidepressants)
- ▶ Risk-Benefit Analysis:
 - Maybe beneficial after indicated antidotes/therapies implemented and no improvement.

Scenarios

- ▶ **Scenario 3:**
- ▶ Patient arrives to ED in cardiac arrest after overdose with lipid soluble drug (CCB, beta blockers, antidepressants)
- ▶ Risk-Benefit Analysis:
 - Maybe beneficial at last line therapy: ACLS + IFE

Scenarios

- ▶ **Scenario 4:**
- ▶ Patient develops decreased mental status after overdose with antidepressants (atypicals and TCAs) or antipsychotics
- ▶ Risk-Benefit Analysis:
 - Likely more risk than benefit: Supportive care and indicated antidotes, monitor for deterioration and reassess risk-benefit

Summary

- ▶ Intravenous Lipid or Fat Emulsion is a new antidote useful in the treatment of select overdoses
- ▶ Consider IFE therapy after severe OD:
 - Local Anesthetics (most available evidence support)
 - Other lipid soluble drugs such as CCB, BB and antidepressants (some evidence)
 - Maybe used as last line therapy during cardiac arrest due to lipid soluble drug OD
- ▶ Dosage is IV bolus followed by infusion

IFE Resources

- ▶ www.lipidrescue.org
 - Dr. Weinberg's site
 - Registry of cases treated with IFE
- ▶ www.aagbi.org/publications/guidelines.htm#m
 - Association of Anesthetists of Great Britain and Ireland Position Statement
- ▶ Picard, J and Meek, T. "Editorial: Lipid emulsion to treat overdose of local anesthetic: the gift of the glob." *Anesthesia* (2006) 61, 107-109
- ▶ Jamaty, C et.al. "Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies." *Clinical Toxicology* (2010) 48,1-27