ILE
INTRAVENOUS LIPID EMULSION THERAPY FOR TOXICITIES

Brian C. Young, VMD, DACVIM (Internal Medicine), DACVECC

Animal Specialty Group

Specialized Treatment + Compassionate Care

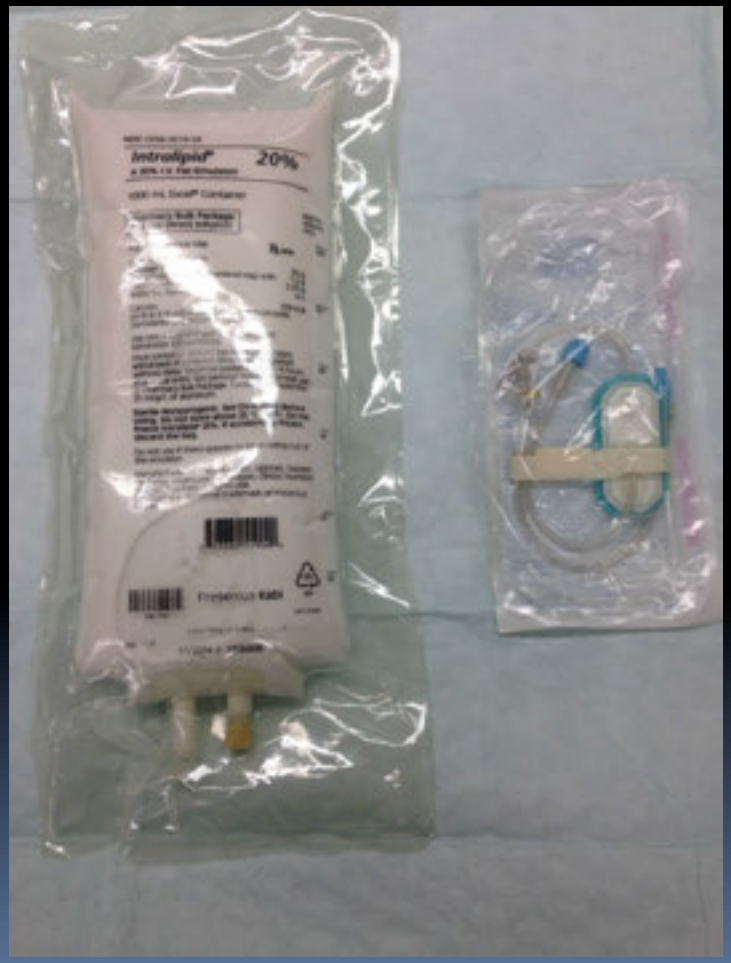
Welcome Dr. Nicole DeNezzo!

Objectives

- Introduce a novel treatment modality for life-threatening toxicoses
- Provide background
- Review human and veterinary literature
- Discuss infusion protocol and adverse effects

Background

- ILE used in human medicine for the past decade to treat local anesthetic overdose
- ILE useful to rescue patients poisoned with lipophilic substances failing traditional therapy

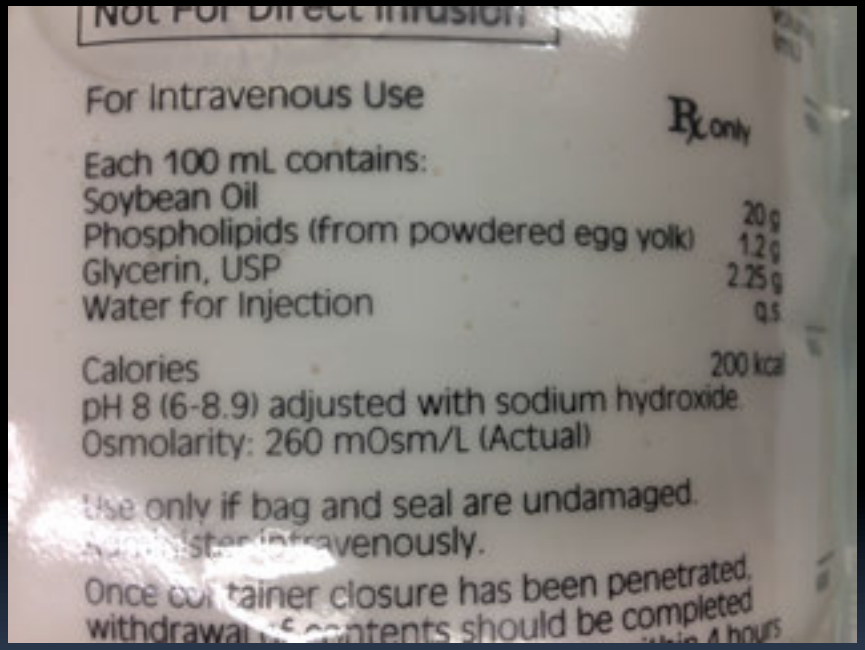


ILE is treatment of choice for local anesthetic systemic toxicosis in humans

- Association of Anesthesiologists of Great Britain and Ireland
- American Society of Critical Care Anesthesiologists
- American Society of Anesthesiologists Committee on Critical Care Medicine
- Resuscitation Council of the UK
- American Society of Regional Anesthesia

Lipid emulsions

- Intralipid 20% solution (10-30%), 500 and 1000 ml bags
- Neutral, medium to long-chain triglycerides derived from plant oils (soybean), egg phosphatides, and glycerin
- Fat droplets similar to endogenous chylomicrons



20% Intralipid

- Component of TPN (mixed with amino acids, dextrose, vitamins and minerals)
- Highly susceptible to bacterial contamination
- Shelf life of two years

Mechanism of action?

1. Sequestration="lipid sink"; lipid forms new compartment
- Supported by visible sequestration of lipophilic dye in a dose-dependent manner
- Dye had same lipid solubility as bupivacaine/lidocaine
- May not explain rapidity of hemodynamic stabilization

Papadopoulou, et al. *Reg Anes & Pain Med* 2012;37(2):183-187.

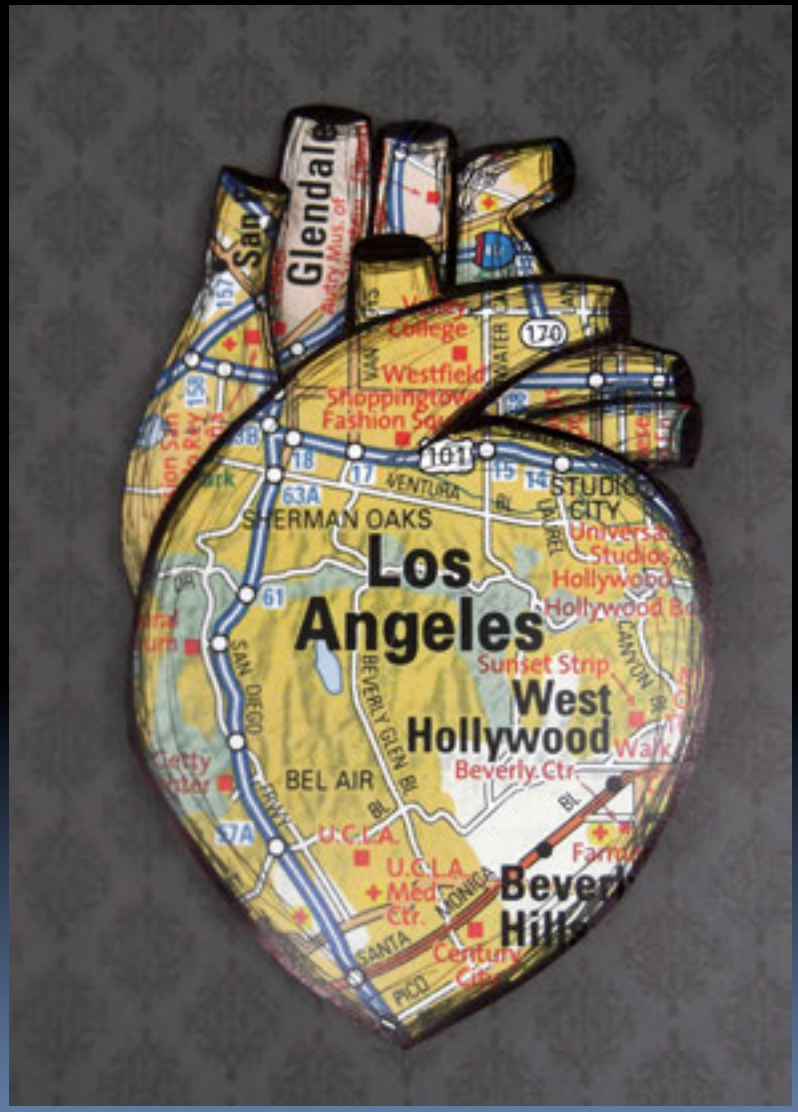
What happens to toxins?

- Peak plasma levels of drug may be observed after ILE (buproprion, ivermectin), supporting lipid sink theory
- Circulating lipoprotein lipase hydrolyzes triglycerides, releasing FFA
- FFA taken up & cleared by skeletal muscle, splanchnic viscera, myocardial, and subcutaneous tissue
- In cells FFA transported to mitochondria via carnitine translocase to undergo beta oxidation, producing ATP
- Toxins are likely degraded in lysosomes

MOA: improved myocardial function

2. Metabolic theory: FFA improve myocardial ATP production and function

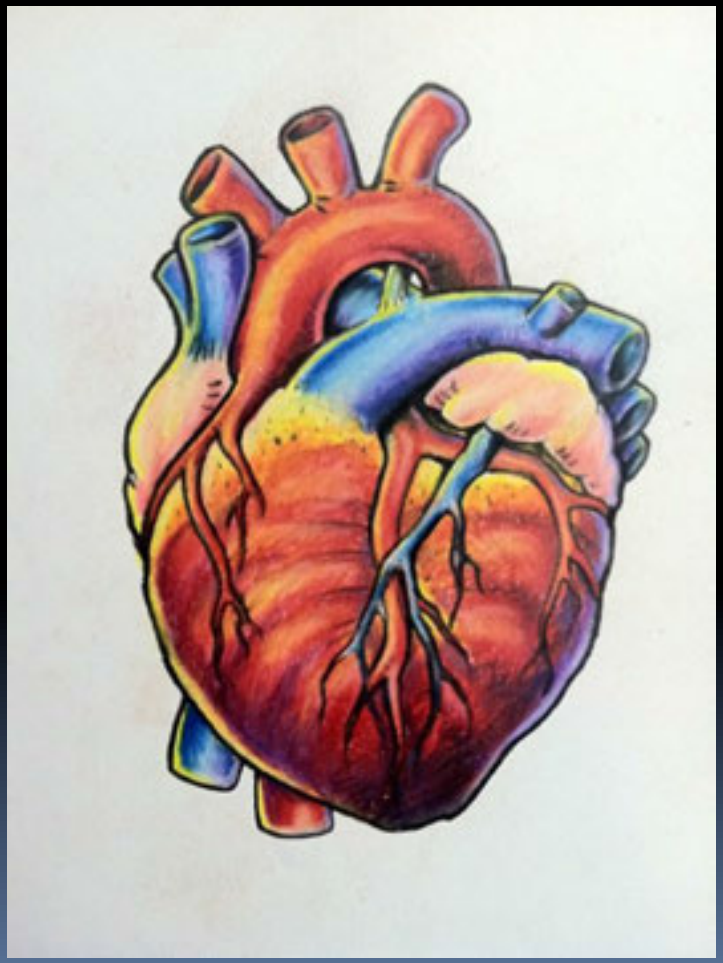
- 80-90% myocardial energy from FFA
- Local anesthetics inhibit FFA from entering mitochondia (carnitine translocase)



Jennifer Korsen, artist

Third mechanism

3. LCFA activate voltage-dependent Ca channels, increase intracellular Ca & inotropy
- This may be detrimental in ischemic tissue



Lipid-soluble toxins

- Local anesthetics (lidocaine, bupivacaine)
- Avermectin parasiticides (ivermectin, moxidectin)
- Beta-blockers
- Ca channel-blockers (diltiazem, amlodipine)
- Digoxin
- Amiodarone
- Baclofen
- Anti-depressants (fluoxetine, sertaline, paroxetine, imipramine, clomipramine, amitriptyline, doxepin, bupropion, trazadone)
- Antihistamines (chlorpheniramine, promethazine, doxepin)
- Chlorpromazine
- Itraconazole
- Loratadine
- Nicotine
- Insecticides (permethrin/pyrethrin, organophosphates, carbamates)
- Illicit drugs (marijuana, methamphetamine, cocaine)
- Anti-epileptic drugs (phenobarbital, lamotrigine, carbamazepine)
- Loperamide
- Bromethalin
- CCNU, vinblastine
- Minoxidil
- Hydrochloroquine
- NSAIDS (carprofen, indomethacin, ketoprofen,naproxen)
- Cyclosporin
- Dexamethasone
- Diazepam
- Haloperidol

Literature review

- Limitations of case reports:
  - correlation does not equal causation
- Randomized, controlled trials needed to evaluate efficacy

Lipid Emulsion Infusion Rescues Dogs From Bupivacaine-Induced Cardiac Toxicity

Guy Weinberg, M.D., Richard Ripper, B.A., Douglas L. Feinstein, Ph.D., and William Hoffman, Ph.D.

- 10 mg/kg bupivacaine IV
- Causes impaired fatty acid oxidation by inhibiting carnitine translocase, blocking ATP production→ negative inotropy/chronotropy
- Cardiopulmonary arrest and CPR x 10 minutes
  - lipid rescue 100% survival (4 ml/kg over 2 minutes followed by 0.5 ml/kg/min x 10 minutes)
  - saline placebo 0% survival
- ILE direct inotropic effects most likely

Reg Anes Pain Med 2003

Moxidectin toxicosis in a puppy successfully treated with intravenous lipids

Dawn E. Crandell, DVM, DVSc, DACVECC and Guy L. Weinberg, MD

- First clinical veterinary case report
- Moxidectin terminal elimination half life in dog 25.9 days
- 16 week-old FI Jack Russell Terrier
- Contact with horses treated with dewormer
- Vomiting, ataxia, seizuring; progressed to coma, bradycardia (HR 60) & hypoventilation (SpO_2 88% $pvCO_2$ 72.3)
- Mechanical ventilation, fluids, diazepam, & activated charcoal given

Crandell and Weinberg *JVECC* 2009

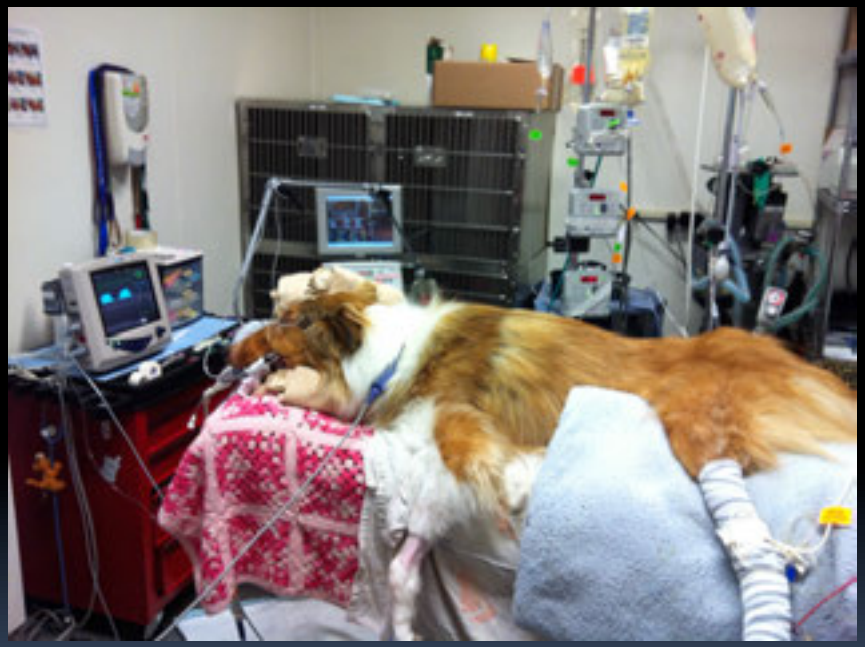
Clinical course

- 5.5 hours post admission: 2 ml/kg ILE, then 4 ml/kg/hr x 4 hours
- Within 2 hours of ILE, RE improved and PPV discontinued, but could not be extubated
- 11 hours after lipids: swallowing & extubated
- 24 hours after toxin exposure: 2nd lipid bolus (15 ml/kg given over 30 minutes)
- 30 minutes later: ambulatory. Behavior improved over next few hours. 6 hours later: ate well, off diazepam CRI with no more seizures

Use of intravenous lipid emulsion to treat ivermectin toxicosis in a Border Collie

Dana L. Clarke, VMD, DACVECC; Justine A. Lee, DVM, DACVECC; Lisa A. Murphy, VMD; Erica L. Reineke, VMD, DACVECC

- 2 year-old FS Border Collie
- Ingested equine dewormer and developed lethargy, ataxia, tremors, blindness
- ABCB1-1Δ polymorphism suspected
- Canine ivermectin toxicities have required long term mechanical ventilation
- 80 hour half life



JVECC 2011;239:1328-1333

Clinical course

- 20% Intralipid 1.5 ml/kg bolus over 10 minutes, CRI 0.25 ml/kg/min for 60 minutes
- 6 hours later: more responsive & ambulatory, remained ataxic
- 12 hours: ILE repeated, after which dog much better, tremors minimal, improved mydriasis
- Discharged & made a full recovery with return of vision

Additional testing

- No ABCB1-1Δ mutation
- Ivermectin blood levels increased immediately after ILE doses, suggesting a lipid sink mechanism
- Ivermectin blood levels decreased over time

Lipid infusion in the management of poisoning: a report of 6 canine cases

N. Bates, J. Chatterton, C. Robbins, K. Wells, J. Hughes, M. Stone, A. Campbell

- 3 ivermectin
- 2 moxidectin
- 1 baclofen
- All dogs improved by 4.5 hours after ILE
- Only adverse effect was swelling and pain due to extravasation of lipids
- All discharged by 52 hours after exposure and made full recoveries

Vet Rec 2013

Treatment of Ibuprofen Toxicosis in a Dog with IV Lipid Emulsion

Luiz Bolfer, DVM, Maureen McMichael, DVM, DACVECC, Thandeka R. Ngwenyama, DVM, Mauria A. O'Brien, DVM, DACVECC

- 3 year-old FS mixed breed dog
- 1856 mg/kg ibuprofen (180 tablets)
- Became obtunded and then comatose, tachycardic, and hypotensive within 30 minutes
- Treatment with prostaglandin analogs, naloxone, and antiemetics
- Clinical signs improved 3 hours after ILE and patient discharged 3 days later

JAAHA 2014

Use of IV Lipid Emulsion for Treatment of Ivermectin Toxicosis in a Cat

James H. Kidwell, BS*, Gareth J. Buckley, MA, VetMB, DACVECC, Ashley E. Allen, DVM, Carsten Bandt, DVM, DACVECC

- 1 y MC DSH ingested equine ivermectin paste
- Laterally recumbent, lethargic, tachycardic, hyperesthetic
- Treated with IV fluids
- 24h later: obtunded, hypothermic, hypoxemic

JAAHA 2014;50:59-61

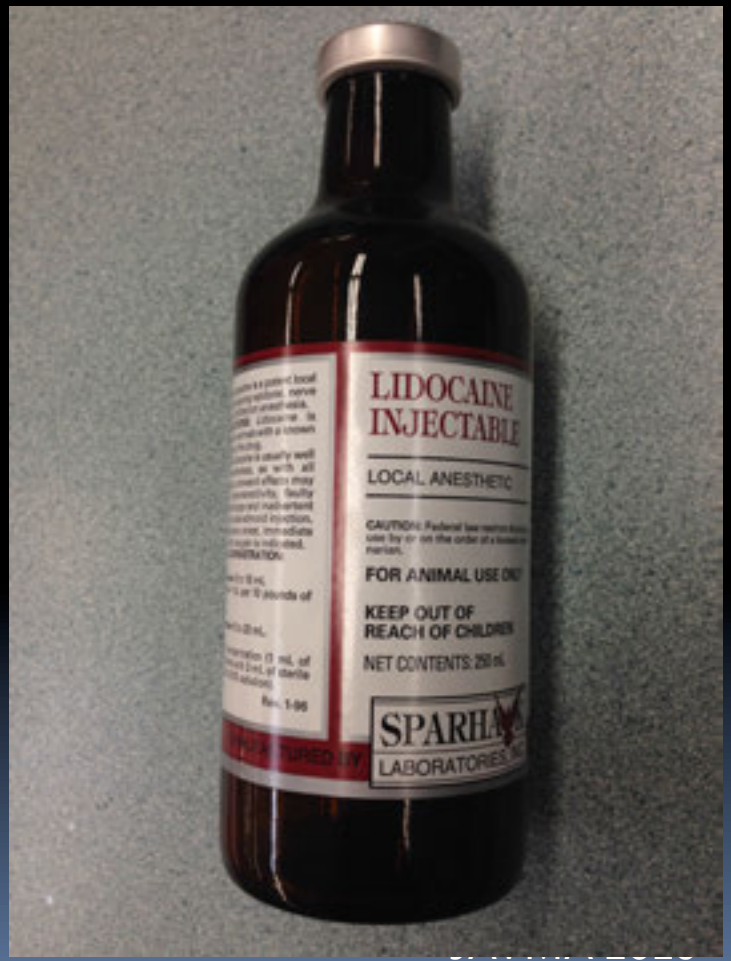
Clinical course

- 4 ml/kg 20% Intralipid; 3 ml/kg/h x4 hours; became lipemic
- 5 hours later: responsive, but remained non-ambulatory
- Next day: 2nd lipid infusion 3 ml/kg/hr x 2 h (lipemia had resolved); began swallowing
- 4 days after ingestion: discharged, mild ataxia resolved at home

Infusion of a lipid emulsion to treat lidocaine intoxication in a cat

Taylor Q. O'Brien, DVM; Stuart C. Clark-Price, DVM, MS, DACVIM, DACVA;
Erika E. Evans, DVM; Renata Di Fazio, DVM; Maureen A. McMichael, DVM, DACVECC

- 5 y MC DSH presented after 20.5 mg/kg SQ lidocaine for wound debridement
- Lethargic, dyspneic, non-responsive, poor perfusion
- 20% Intralipid 3 ml/kg over 60 minutes
- Patient became more responsive within 15 minutes
- Made a full recovery



Intravenous lipid emulsion for treating permethrin toxicosis in a cat

- 2 year-old cat
- Seizures, tremors, hypersalivation after permethrin toxicity
- Treated with bathing, methocarbamol, and ILE
- Recovered and discharged in 42 hours

Can Vet J 2014

Animal studies

- Yoav 2002: significantly lower mortality in rats poisoned with clomipramine receiving ILE vs saline
- Harvey 2007: faster recovery of BP in clomipramine rabbit toxicity
- Bania 2007: showed improved survival with ILE vs saline (7/7 vs 1/7) in dogs poisoned with verapamil

Human case reports

- Cardiopulmonary arrest (4-20 minutes) in three patients with local anesthetic overdose.
  - Successfully rescued with ILE[1-3]
  - All survived and fully recovered

1. Rosenblatt *Anesthesiology* 2006 2. Litz *Anaesthesia* 2006 3. Foxall *Anaesthesia* 2007

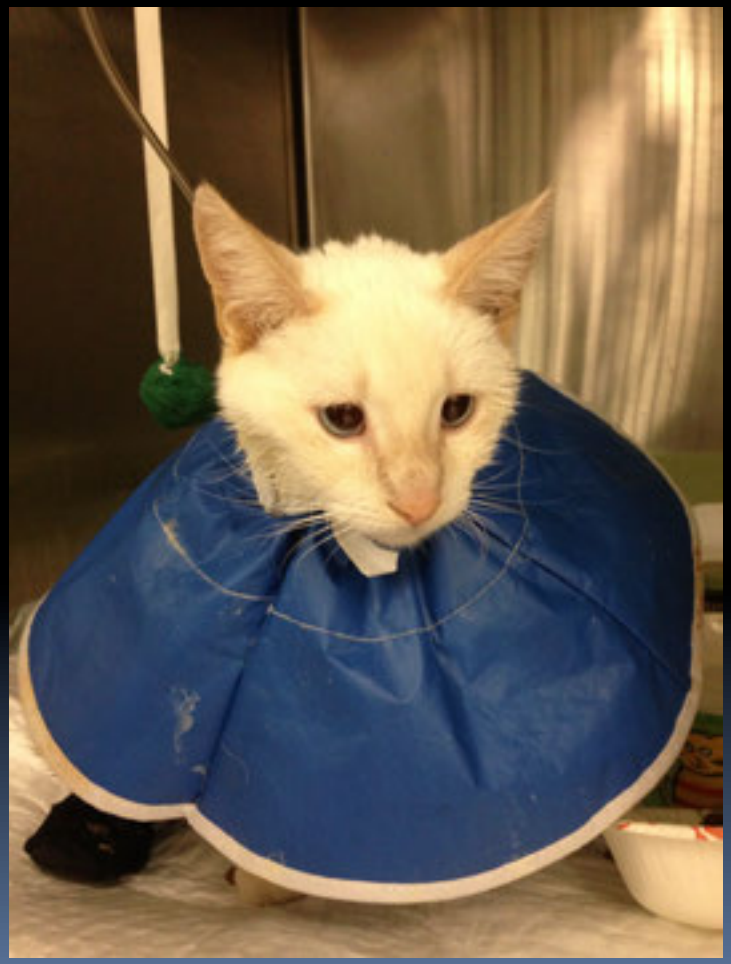
Human literature

- Person overdosed on bupropion, comatose, suffered cardiopulmonary arrest x50 minutes and was successfully resuscitated with ILE
  - Serial blood levels of buproprion consistent with lipid sink (higher after infusion)

Sirianni *Ann Emerg Med* 2008

Evidence-based?

- Lack of prospective, randomized trials
- Outcome difficult to attribute to ILE vs other treatment measures
- Considered "experimental" at this time and should be **reserved for severe intoxications**
- Used *in addition to* **not** instead of traditional therapies



Infusion protocol

*as recommended by ASPCA Animal Poison Control

- Requires a dedicated IV catheter (do not mix with fluids)
- Aseptic technique (gloves to prepare infusion)
- *Only* **20% solution**, through a 1.2 micron **TPN filter**
- 1.5 ml/kg over 5 minutes
- 0.25 ml/kg/min for 30-60 minutes
- Repeat in four hours if no **lipemia** (spin down hematocrit tubes); do not repeat if serum orange or yellow
- Limit of 8 ml/kg/d
- Refrigerate between uses
- Discard bag 24 hours after opening

Filter?

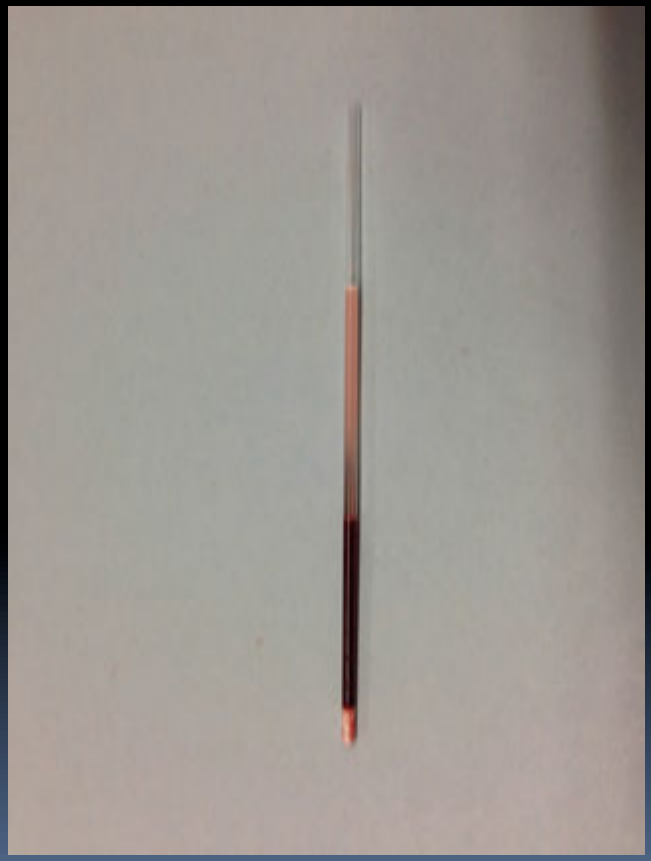
- Filter out small particles that may lead to fat emboli
- Trap any air bubbles present

Recurrent toxicity

- Cardiotoxicity may recur after ILE infusion
  - Toxin may come out of lipid solution or may not be fully taken up
  - Toxin may be released as lipid is metabolized
- Monitor patients and consider repeating ILE if clinical signs recur

Adverse effects

- **Major adverse effects are RARE**
- Lipemia
- Possible pancreatitis secondary to lipemia
- Interference with therapeutic drugs: anti-convulsants, insulin
- Immune cell dysfunction secondary to lipids
- May worsen oxygenation in ARDS patients



Adverse effects

- Hypersensitivity reactions to soybean or egg protein:
  - fever, nausea, vomiting within 20 minutes
- Lipid emboli, thrombosis, thrombocytopenia
- Laboratory errors:
  - false elevation of glucose, methemoglobin
  - affects AST, amylase, phosphorus, creatinine
- Fat overload syndrome--hyperlipidemia with:
  - hemolysis, jaundice, seizures, prolonged clotting time, thrombocytopenia, fat embolism
- Lipids promote bacterial growth
- Phlebitis
- Safety studies LD50 in rats 68 ml/kg!

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Thank you! Questions?