Lipid Resuscitation: Foundations and Future

EAPCCT, Madrid
27 May, 2016

GL Weinberg, MD
U of Illinois
Jesse Brown VA
Chicago, IL
DISCLOSURES:
1. US Patent related to lipid resuscitation
2. Established www.lipidrescue.org
4. Off label use of an FDA approved medication
ACMT Position Statement: Guidance for the Use of Intravenous Lipid Emulsion

American College of Medical Toxicology

Recommended Guideline

Given the uncertainty of its beneficial effect in human poisonings, it is the opinion of the American College of Medical Toxicology that there are no standard of care requirements to use, or to choose not to use, ILE. However, in circumstances where there is serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, ILE is viewed as a reasonable consideration for therapy.
Focus Today on Lipid Resuscitation

- Development
- Efficacy
- Mechanism
- Controversies
- Future
Development of Lipid Resuscitation
For LAST
Classic Treatments for LAST Have Miserable Outcomes
Historical Recognition of LAST

Mayer E. The Toxic Effects Following the Use of Local Anesthetics. JAMA, 1924.

43 unpublished cases of fatal toxicity involving ENT cases.

Volume 51, No. 4
October 1979

The Journal of Anesthesiology
The American Society of Anesthesiologists, Inc.

Editorial Views

Cardiac Arrest Following Regional Anesthesia with Etidocaine or Bupivacaine

Six fatalities following bupivacaine or etidocaine
A CLINICAL NIGHTMARE

32 yo ASA Class I male; ORIF of fractured metacarpal
Axillary block with 40mL 0.5% ROPIVICAINE with 1:200,000 Epi
PLUS intercostal brachialis with 5mL
Tonic-Clonic Seizures -> bradycardia -> apnea -> V Fib
Code Blue: intubation, ACLS protocol X 2 hour
CONSENT FORM
Authorization for Donation of Anatomical Gifts

1. I authorize LifeShare Of The Carolinas to utilize such personnel and services as in their judgment may appear necessary for the purposes for which this Authorization is granted. Any persons or organizations so utilized may rely on this authorization.

2. I, as next-of-kin of the above named decedent, in the hope that I may help others, hereby donate and permit the removal of the following organs and tissues: (ENTER YES OR NO)

<table>
<thead>
<tr>
<th></th>
<th>Heart</th>
<th>Kidneys</th>
<th>Liver</th>
<th>Lungs</th>
<th>Pancreas</th>
<th>Intestines</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>Heart for Valves</td>
<td>Whole Eyes</td>
<td>Leg Veins</td>
<td>Whole Body</td>
<td>Corneas</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Bone/Associated Tissue of upper extremities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the donated gifts are not able to be transplanted, I authorize LifeShare Of The Carolinas and other persons or organizations responsible for the following (lymph nodes and spleen) needed for laboratory tests to determine and if ordered, and that in the case of brain death, artificial support will be continued.

3. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

4. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

5. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

6. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

7. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

8. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

9. I, as next-of-kin, agree to the removal of the following (lymph nodes and spleen) needed for laboratory tests to determine

10. I understand that if bone is to be donated an unlimited autopsy may be performed, and I have no objections to this.

Signed: ____________________________

11. I understand that no costs associated with evaluation, management, and/or surgical retrieval will be incurred by the donor's family or estate. Any expenses incurred up until death determination (or brain death) will continue to be the responsibility of the estate.

12. This document has been explained to me by: ____________________________

13. I make this gift voluntarily and with full understanding of this document.
“Spa Gel” Death

Student's Death Sparks Concerns About Compounded Preparations

BETHESDA, MD, 14 February 2005 —22-year-old college student died after having an adverse reaction to a potent anesthetic gel prepared by a pharmacy and sold to a so-called medical spa, which resold the product to the patient without a prescription.

Shiri Berg had a seizure in her car on December 28, 2004, after applying a topical gel containing 10% lidocaine, 10% tetracaine, and an unknown amount of phenylephrine, said Gail Campbell, a nurse employed by Kirby & Holt, a Raleigh law firm founded by former Senator John Edwards.
Rochester Death Halts MIT-Funded Study

Case Report on Death of University of Rochester Student.

19 year old Nicole Wan was participating in a research project that involved bronchoscopy on healthy volunteers. She collapsed at home shortly after undergoing bronchoscopy and died two days later. The facility reported and the medical examiner confirmed and the blood level of lidocaine in the emergency room (9mcg/mL) indicated she received more than four times the amount of lidocaine than the maximum dosage established in the research protocol. The student's family plans to file a $100 million lawsuit, according to Reuters.
Girl, 17, dies during wisdom teeth surgery

By RACHEL QUIGLEY
UPDATED: 12:01 EST, 15 December 2011

The parents of a teenager who died after having her wisdom teeth removed are suing the oral surgeon and anesthetist for medical malpractice.

Jenny Olenick, 17, from Maryland, went in for the surgery - which is performed on five million Americans a year - in April and died from complications during the routine procedure.

Her parents have filed a civil lawsuit claiming the surgeon Dr Domenick Coletti and anesthesiologist Dr Krista Michelle were negligent and failed to resuscitate the 17-year-old after her heart rate and blood oxygen level dropped.

Mother Cathy Garger told ABC: 'It's so hard. She was the only one we had.'

Her cause of death at the time was ruled as hypoxia - oxygen deprivation while she was anesthetized.

Jenny Olenick, a 17-year-old junior at Marriotts Ridge High School, died in April from complications during surgery.
Kensley Kirby, 5-Year-Old Atlanta Girl, Dies From Lethal Dose Of Local Anesthetic
Lawsuit filed in furniture company owner's death

4:54 PM, Oct 23, 2008 | comments

LESLIE FISHBEIN

Courtesy: Blacktie-Colorado.com

Liltie Aramayo / USA TODAY

5:30 PM, Oct 23, 2008 | 1,108 replies | 100 shares

Leslie Fishbein was the owner of Leslie's Furniture in Colorado.
20 yo patient with isovaleric acidemia: During SQ injection of bupivacaine, he develops arrhythmia with systolic BP 70, then complete heart block, then VT.

Bupivacaine dose = 22mg.

Patient is severely carnitine deficient

IS THERE A CARNITINE CONNECTION?

[Chemical structure of carnitine]

Biochemical Properties of Subsarcolemmal and Interfibrillar Mitochondria Isolated from Rat Cardiac Muscle*

(Received for publication, July 29, 1977)

June W. Palmer, Bernard Tandler, and Charles L. Hoppel

From the Veterans Administration Hospital and Departments of Pharmacology and Medicine, School of Medicine, and the Department of Oral Biology and Medicine, School of Dentistry, Case Western Reserve University, Cleveland, Ohio 44106

REQUIRED FOR FATTY ACID TRANSPORT INTO MITOS AND ATP SYNTHESIS FROM HEART’S PREFERRED FUEL
Bupivacaine Inhibits Acylcarnitine Transport

Weinberg, G, Palmer J, VadeBoncouver, T and Hoppel, C. Anesthesiology, 2000; 92:523-528
And then an unexpected finding........
Control vs. Lipid Rescue (15mg/kg)

Weinberg G, VadeBoncouerT, Ramaraju, G Garcia-Amaro M, Cwik, M
Anesthesiology, 1998
Bupivacaine-Induced Asystole, Lipid-Based Rescue

Isolated Heart Model
A heart burning lipid is far more sensitive to bupivacaine than when burning carbohydrate alone.

Lipid Improves Isolated Heart Function in Bupivacaine Toxicity

Stehr et al, AA, 2007
Translation of laboratory findings to the clinical setting

... the first successful use of Lipid

Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest

Meg A. Rosenblatt, M.D.,* Mark Abel, M.D.,† Gregory W. Fischer, M.D.,† Chad J. Itzkovich, M.D.,‡ James B. Eisenkraft, M.D.§

INTERSCALENE BLOCK  20ml Bupivacaine 0.5% - 20ml Mepivacaine 1.5%
Within 30 sec seizures (Propofol 50+100mg); 90 sec later CARDIAC ARREST…
CPR,O2-ventilation,epinephrine,atropine,amiodarone,vasopressin, defibrillation…
PULSELESS VT… Within 15 sec OF LIPID pulse/blood pressure detectable

YES!!
Meg Rosenblatt saves the day
CASE REPORT
Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion*

R. J. Litz, M. Popp, S. N. Stehr and T. Koch

CASE REPORT
Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid®

G. Foxall, R. Mcahan, J. Lamb, J. G. Hardman and N. M. Bedforth

Kardio- und neurotoxische Nebenwirkungen nach akzidenteller intravasaler Bupivacainapplikation
Therapie mit Lidocain, Propofol und Lipidemulsio

Lipid Reversal of Central Nervous System Symptoms of Bupivacaine Toxicity
Andrew G. Spence, F.R.C.A., King Edward VII Memorial Hospital, Hamilton, Bermuda. aspence@transact.bm
Eight More Cases in 2008
4 in Anesthesia and Analgesia; 4 in RAPM
20% lipid infusion at 3ml/kg

After block

2 min after infusion

Case Report

Successful resuscitation of bupivacaine-induced cardiotoxicity in a neonate

ERICA P. LIN MD AND LORI A. ARONSON MD

Department of Anesthesiology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA
In summary, there is convincing anecdotal and experimental evidence that IFE is effective in treating toxicity caused by local anesthetics.

"..Current evidence suggests that IFE should be administered as soon as a diagnosis of local anesthetic toxicity is established, ..."
AAGBI Safety Guideline
Management of Severe Local Anaesthetic Toxicity

1 Recognition

- Signs of severe toxicity:
  - Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions
  - Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
  - Local anaesthetic (LA) toxicity may occur some time after an initial injection

2 Immediate management

- Stop injecting the LA
- Call for help
- Maintain the airway and, if necessary, secure it with a tracheal tube
- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Assess cardiovascular status throughout
- Consider drawing blood for analysis, but do not delay definitive treatment to do this

3 Treatment

IN CIRCULATORY ARREST

- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory to treatment
- Consider the use of cardiopulmonary bypass if available

GIVE INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1 h
- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

WITHOUT CIRCULATORY ARREST

Use conventional therapies to treat:
- hypotension,
- bradycardia,
- tachyarrhythmia

CONSIDER INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

4 Follow-up

- Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved
- Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days
- Report cases as follows:
  - In the United Kingdom to the National Patient Safety Agency (via www.npsa.nhs.uk)
  - In the Republic of Ireland to the Irish Medicines Board (via www.imb.ie)
- If Lipid has been given, please also report its use to the international registry at www.lipidregistry.org. Details may also be posted at www.lipidrescue.org

Your nearest bag of Lipid Emulsion is kept
Practice Advisory on Treatment of Local Anesthetic Systemic Toxicity

For Patients Experiencing Signs or Symptoms of Local Anesthetic Systemic Toxicity (LAST)

- Get Help
- Initial Focus
  - Airway management: ventilate with 100% oxygen
  - Seizure suppression: benzodiazepines are preferred
  - Basic and Advanced Cardiac Life Support (BLS/ACLS) may require prolonged effort
- Infuse 20% Lipid Emulsion (values in parenthesis are for a 70 kg patient)
  - Bolus 1.5 mL/kg (lean body mass) intravenously over 1 min (~100 mL)
  - Continuous infusion at 0.25 mL/kg/min (~18 mL/min; adjust by roller clamp)
  - Repeat bolus once or twice for persistent cardiovascular collapse
  - Double the infusion rate to 0.5 mL/kg per minute if blood pressure remains low
  - Continue infusion for at least 10 mins after attaining circulatory stability
  - Recommended upper limit: approximately 10 mL/kg lipid emulsion over the first 30 mins
- Avoid vasopressin, calcium channel blockers, β-blockers, or local anesthetic
- Alert the nearest facility having cardiopulmonary bypass capability
- Avoid propofol in patients having signs of cardiovascular instability
- Post LAST events at www.lipidrescue.org and report use of lipid to www.lipidregistry.org
Part 12: Cardiac Arrest in Special Situations
2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Terry L. Vanden Hoek, Chair; Laurie J. Morrison; Michael Shuster; Michael Donnino; Elizabeth Sinz; Eric J. Lavonas; Farida M. Jeejeebhoy; Andrea Gabrielli

This section of the 2010 AHA Guidelines for CPR and ECC addresses cardiac arrest in situations that require special treatments or procedures beyond those provided during basic life support (BLS) and advanced cardiovascular life support (ACLS). We have included 15 specific cardiac arrest situations. The first several sections discuss cardiac arrest associated with internal physiological or metabolic conditions, such as asthma (12.1), anaphylaxis (12.2), pregnancy (12.3), morbid obesity (12.4), pulmonary embolism (PE) (12.5), and electrolyte imbalance (12.6).

The next several sections relate to resuscitation and treatment of cardiac arrest associated with external or environmentally related circumstances, such as ingestion of toxic substances (12.7), trauma (12.8), accidental hypothermia (12.9), avalanche (12.10), drowning (12.11), and electric shock/lightning strikes (12.12).

The last 3 sections review management of cardiac arrest that may occur during special situations affecting the heart, including percutaneous coronary intervention (PCI) (12.13), cardiac tamponade (12.14), and cardiac surgery (12.15).

Part 12.1: Cardiac Arrest Associated With Asthma
Asthma is responsible for more than 2 million visits to the

Pathophysiology
The pathophysiology of asthma consists of 3 key abnormalities:

- Bronchoconstriction
- Airway inflammation
- Mucous plugging

Complications of severe asthma, such as tension pneumothorax, lobar atelectasis, pneumonia, and pulmonary edema, can contribute to fatalities. Severe asthma exacerbations are commonly associated with hypercarbia and acidemia, hypotension due to decreased venous return, and depressed mental status, but the most common cause of death is asphyxia. Cardiac causes of death are less common. 4

Clinical Aspects of Severe Asthma
Wheezing is a common physical finding, although the severity of wheezing does not correlate with the degree of airway obstruction. The absence of wheezing may indicate critical airway obstruction, whereas increased wheezing may indicate a positive response to bronchodilator therapy.

Oxygen saturation (SaO₂) levels may not reflect progressive alveolar hypventilation, particularly if oxygen is being administered. Note that SaO₂ may fall initially during therapy because β₂-agonists produce both bronchodilation and vasodilation and
How does the efficacy of lipid resuscitation compare to standard, pressor-based resuscitation for LAST?
What about Pressors?

(mean±SEM) Lipid versus Vasopressin (*), Lipid versus Epinephrine-Vasopressin (+), Lipid versus Epinephrine (#). Three symbols: P<0.001
Lipid versus Vasopressin (*), Lipid vs Epinephrine-Vasopressin (+) and Lipid vs Epinephrine (#).

One symbol: P<0.05
Two symbols: P<0.01;
Three symbols: P<0.001
Lipid versus Vasopressin (*), Lipid vs Epinephrine-Vasopressin (+) and Lipid vs Epinephrine (#).
One symbol: P<0.05; Three symbols: P<0.001
Lipid vs Pressors

Lipid

Epi

ADH
Epinephrine Impairs Outcome

Standard dose in human ~15mcg/kg
Resuscitation with Lipid Emulsion

*Dose-dependent Recovery from Cardiac Pharmacotoxicity Requires a Cardiotonic Effect*

Michael R. Fettiplace, M.S., Belinda S. Akpa, Ph.D., Richard Ripper, C.V.T., Brian Zider, B.S., Jason Lang, B.S., Israel Rubinstein, M.D., Guy Weinberg, M.D.
Lipid Rescue in a Pediatric Burn Patient

Matthew Musielak, MD,* and John McCall, MD†

Pain control is a major concern for patients suffering burns. The addition of bupivacaine to the donor site infiltration solution containing epinephrine could offer a safe and effective means to treat postanesthesia pain. Despite the addition of epinephrine to localize the effects, systemic absorption occurs, and there exists the possibility of inadvertent intravascular injection, with potential CNS and cardiac toxicity. The patient is a 6-year-old boy who sustained flame burns to bilateral lower extremities and buttocks. A Pitkin’s solution containing 2 mg epinephrine/L of normosol and a 0.5% bupivacaine at 3 mg/kg was injected. Shortly after the patient became bradycardic with decreasing end tidal CO₂. Pediatric advanced life support protocol was begun. He underwent 30 minutes of cardiopulmonary resuscitation. At this time, intralipid therapy was initiated with a 1.5 mg/kg bolus. Shortly after therapy, a pulse was regained. It had been previously demonstrated that the addition of bupivacaine to a subcutaneous infiltrating solution for donor site harvesting was a safe and effective treatment of pain for skin graft harvesting. Care must be taken to stay within the therapeutic allotted dose. Inadvertent intravascular injection is a rare complication. Early recognition of clinical signs of local anesthetic toxicity is a key to the management and treatment. A lipid protocol should be in place, given the many positive case reports of local anesthetic toxicity. Surgeon judgment must be used when weighing the risks and benefits of pain control during skin harvesting vs the potential cardiac effects with local anesthetics. (J Burn Care Res 2015;XXX:00–00)
Successful resuscitation from bupivacaine-induced cardiovascular collapse with intravenous lipid emulsion following femoral nerve block in an emergency department

Martyn Harvey, Grant Cave, Giles Chanwai and Tonia Nicholson

1 Waikato Hospital, Hamilton and 2 Hutt Hospital, Lower Hutt, New Zealand
clamped and extracorporeal circulation initiated. After concluding the valve replacement and 20 minutes after the second infusion of the cardioplegic agent, the heart showed no electrical activity. After a few minutes of internal cardiac massage, ventricular fibrillation occurred, but was refractory to internal cardiac massage used in combination with various defibrillation attempts. This situation persisted for 20 minutes until the inadvertent substitution of lidocaine for 0.5% bupivacaine (100 mg) in the cardioplegic solution was identified as the cause. This solution had been injected directly into the coronary ostium.

An infusion of 20% lipid emulsion was requested; however, only the 10% solution was available in the hospital. After an intravenous injection of a 90 ml bolus (1.5 ml/kg) of this emulsion, approximately 40 minutes after the final dose of the cardioplegic agent, defibrillation was repeated, leading to immediate reversal of ventricular fibrillation.
Local infiltration by the surgeon using 6 ml 0.25% bupivacaine plain for postoperative analgesia. Just after we noticed a fall in the heart rate on the ECG monitors. Immediately, atropine 0.2 mg IV was given. For a while, the heart rate improved but again within 10 seconds, it fell abruptly and the patient went into cardiac asystole. Cardiopulmonary resuscitation (CPR) was started according to the pediatric advanced life support (PALS) guideline 2010. We continued CPR for 60 minutes. Adrenaline was given as soon as asystole was detected and it was repeated. Amiodarone was also given but the patient could not be revived despite all these efforts.

Not all bias is positive:
So, what will you do?....

Now, non-LAST
>90 Minutes Total CPR

1min after 100mL lipid, ROSC, CPR stopped, QRS narrows. Patient recovers, neurologically intact.
Modeling Bupropion Toxicity

Chart Window

Systolic Pressure (mmHg)

bupropion 10mg/kg/min iso off stopped CPR lipid in repeat IL 10mL/kg start infusion .2mL/min

Timeline:
- 31:40
- 33:20
- 35:00
- 36:40
- 38:20
- 40:00

Pressure Levels:
- 8
- 9
- 10
- 11
- 12
- 13
- 14

Arrows indicate significant events.
Use of Lipid Emulsion in the Resuscitation of a Patient With Prolonged Cardiovascular Collapse After Overdose of Bupropion and Lamotrigine

Archie J. Sirianni, MD
Kevin C. Osterhoudt, MD
Diane P. Calello, MD
Allison A. Muller, PharmD
Marie R. Waterhouse, MD
Michael B. Goodkin, MD
Guy L. Weinberg, MD
Fred M. Henretig, MD

From the Department of Anesthesiology (Sirianni) and Division of Cardiology (Goodkin), Riddle Memorial Hospital, Media, PA; the Department of Pediatrics, University of Pennsylvania School of Medicine and The Children’s Hospital of Philadelphia, Philadelphia, PA (Osterhoudt, Calello, Muller, Waterhouse, Henretig); the Section of Clinical Toxicology, Division of Emergency Medicine, and the Poison Control Center, The Children’s Hospital of Philadelphia, Philadelphia, PA (Osterhoudt, Calello, Muller, Henretig); and the Department of Anesthesiology, University of Illinois College of Medicine at Chicago, and Jessie Brown VA Medical Center, Chicago, IL (Weinberg).

Animal studies show efficacy of intravenous lipid emulsion in the treatment of severe cardiotoxicity associated with local anesthetics, clomipramine, 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 parenteral administration of local anesthetics, but clinical evidence has been lacking for lipid’s antidotal efficacy on toxicity caused by ingested medications. A 17-year-old girl developed seizure activity and cardiovascular collapse after
Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose
Amy C. Young, Larissa I. Velez, Kurt C. Kleinschmidt

CASE REPORT
Early treatment of a quetiapine and sertraline overdose with Intralipid
K. Tamir and N. Sable

Tricyclic Antidepressant Overdose in a Toddler Treated With Intravenous Lipid Emulsion
Paul T. Engels, Jonathan S. Davidow

Usefulness of Intravenous Lipid Emulsion for Cardiac Toxicity from Cocaine Overdose
Natasha Purai Arora, MD, William Allen Berk, MD, Cynthia Kurke Aaron, MD, and Kim Allan Williams, MD
Figure 1. Initial electrocardiogram showing wide-complex tachycardia (heart rate 143 beats/min), QRS duration 142 ms, and corrected QT interval of 595 ms.

Figure 3. Electrocardiogram immediately after infusion of ILE showing regular sinus rhythm (heart rate 118 beats/min) with normal QRS (82 ms) and corrected QT (412 ms) intervals.
Fig. 1. Vasopressor doses and lactate levels.

Amitriptyline overdose
A 10-kg, 20-month-old girl presented to the emergency department 1 hour after ingesting her grandmother's medication, including **45 mg/kg dosulepin**. The patient drowsy but responsive to voice and had obvious nystagmus. She developed a tonic-clonic seizure and, despite rectal and intravenous administration of diazepam, her seizures persisted. The patient's QRS complexes began to broaden progressively despite the administration of a sodium bicarbonate infusion.\(^1\) The patient developed ventricular tachycardia with a rate of 180 beats per minute, although her systolic blood pressure (measured through invasive monitoring) was maintained at 80 mm Hg. In the presence of ongoing deterioration despite exhaustion of national guidelines on managing pediatric TCA overdoses, an intravenous lipid emulsion (ILE) was administered, in light of recent case reports on its successful use for treatment of TCA toxicity among adults.\(^2\)

A bolus dose of 10 mL of ILE (1 mL/kg) (Intralipid, 20% [Fresenius Kabi, Warrington, England]) was administered, followed by an infusion of 150 mL/hour (0.25 mL/kg per minute). **Within minutes after administration of the ILE, the patient's QRS complexes began to narrow.** Her heart rate continued to increase; when it was >200 beats per minute, her blood pressure decreased to 60/30 mm Hg. A synchronized direct-current shock of 50 J was delivered (**Fig. 1**), and narrow-complex sinus tachycardia (150 beats per minute) was immediately restored (**Fig. 2**), which was associated with return of the baseline blood pressure. **Table 1** lists the arterial blood gas findings.
Case report: successful lipid resuscitation in multi-drug overdose with predominant tricyclic antidepressant toxidrome

Martyn Harvey¹* and Grant Cave²
HALOPERIDOL-induced Torsades… antipsychotics, prolongation QT duration and sudden cardiac death

12 min of CPR
1 min after LIPID
Normal vital signs

“LIPID RESCUE” FOR TRICYCLIC ANTIDEPRESSANT CARDIOTOXICITY

Michael Stephen Blaber, mbcchb, * Jamal Nasir Khan, MRCP, † Judith Anne Brebner, MRCP, ‡ and Rachel McCollm, MRCP§


100 mL of 20% lipid-emulsion administered
Narrowing of ECG complexes seen, normalization of pH achieved, improvement of blood pressure (168/86), patient stabilised and transferred to ICU

100 mL of 20% lipid-emulsion administered
Narrowing of ECG complexes seen, normalization of pH achieved, improvement of blood pressure (168/86), patient stabilised and transferred to ICU
Two Lessons from the Empiric Management of a Combined Overdose of Liraglutide and Amitriptyline

Matthew Bowler, BSc, MBChB, MRCPCH, and Daniel Robert Nethercott, BSc, MBBCh, FRCA, DICM, FFICM

A&A Case Reports. 2014;2:28–30

PEA, epi, VT, cardioversion, CPR HCO3, Ca, cardioversion, ST BP60, lac 13, QRS wide 100mL lipid

was given as advised by Toxbase. The QRS complexes normalized, and the patient’s arterial blood pressure increased to 116/64 mm Hg (without any vasoactive support) almost immediately after the loading dose of lipid emulsion (Fig. 2).
## LIPAEOMIC Report: Results of Clinical Use of Intravenous Lipid Emulsion in Drug Toxicity Reported to an Online Lipid Registry

Grant Cave · Martyn Harvey · Johann Willers · David Uncles · Tim Meek · John Picard · Guy Weinberg


### Table 5 Patient characteristics and details of ingestants for non-local anaesthetic drug poisoning, use in cardiovascular collapse

<table>
<thead>
<tr>
<th>Number</th>
<th>Age</th>
<th>Gender</th>
<th>Weight</th>
<th>Intoxicant</th>
<th>Toxicity</th>
<th>Hrs post</th>
<th>Treatments before ILE</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>75</td>
<td>Verapamil SR 9,640 mg</td>
<td>Cardiovascular collapse</td>
<td>36</td>
<td>Calcium, sodium bicarbonate, noradrenaline</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>M</td>
<td>80</td>
<td>Amitriptyline 4.25 g</td>
<td>Hemodynamic instability hours after cardiac arrest</td>
<td>6</td>
<td>Adrenaline, noradrenaline, sodium bicarbonate</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>M</td>
<td>75</td>
<td>Amitriptyline &gt;2 g; quetiapine NK; citalopram NK; quinapril NK</td>
<td>Cardiovascular collapse; ECG abnormality</td>
<td>1.5</td>
<td>Charcoal, sodium bicarbonate</td>
<td>Yes</td>
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<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>70</td>
<td>Metoprolol NK; accupril NK; furosemide NK; amlodipine NK</td>
<td>Cardiovascular collapse; ECG abnormality</td>
<td>4</td>
<td>Noradrenaline, adrenaline, calcium, glucagon</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Dothiepin 450 mg; amlodipine 20 mg</td>
<td>Cardiovascular collapse; VT</td>
<td>2</td>
<td>Charcoal, sodium bicarbonate, calcium</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>F</td>
<td>61</td>
<td>Propafenone NK</td>
<td>Cardiovascular collapse; cardiac arrest</td>
<td>4</td>
<td>Adrenaline, dopamine, sodium bicarbonate, calcium</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>76</td>
<td>Propranolol 600–900 mg; methocarbamol NK</td>
<td>Cardiovascular collapse</td>
<td>5</td>
<td>Noradrenaline, adrenaline, glucagon</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>M</td>
<td>93</td>
<td>Quetiapine &gt;2 g</td>
<td>Cardiovascular collapse; wide complex tachycardia</td>
<td>2</td>
<td>Noradrenaline, adrenaline</td>
<td>No</td>
</tr>
</tbody>
</table>

NR not reported, NK not known, LOC loss of consciousness, VT ventricular tachycardia, u international units, Hrs post interval between ingestion and start ILE (hour)
Zipper, a 3.5 kg puppy ate a fatal dose of moxidectin, a commonly used parasiticide. The puppy exhibited tremors, seizures, then coma + severe respiratory depression requiring ventilation.

Lipid emulsion 1.5 ml/kg bolus and 0.25 mL/kg/min x 30 min. Extubated within 60 minutes, barking and eating. Complete recovery within 24 hours.
There was a significant difference (P = 0.006) between control and ILE-treated cats in the time from presentation to achievement of clinical Stage B (or A), with a mean time of 16.2 hours (95% CI 9.1–23.3 hours) and 5.5 hours (95% CI 1.6–9.5 hours), respectively.
Mechanisms
SPONGE~SINK?

Mazoit et al, Anesthesiology 2009
This is *in vitro* experiment shows very rapid drop of ‘free’ (nonlipid-bound) local anesthetic concentration in 1% solutions of Intralipid or Medialipid over time. The starting concentrations of both local anesthetics is 125mg/L. Intralipid binds more anesthetic than Medialipid and each lipid binds more bupivacaine than ropivacaine.
Lipid Infusion Accelerates Removal of Bupivacaine from Myocardium

Rapid Cardiotonic Effects of Lipid Emulsion Infusion

Michael R. Fettiplace, MS1-3; Richard Ripper, CVT2; Kinga Lis4; Bocheng Lin, MBA4; Jason Lang, BS5; Brian Zider, BS1; Jing Wang, PhD6; Israel Rubinstein, MD3,7; Guy Weinberg, MD2,3

The Effect of Lipid Emulsion on Pharmacokinetics and Tissue Distribution of Bupivacaine in Rats

Kejian Shi, MD,* Yun Xia, MD, PhD,† Quanguang Wang, MD,* Yiquan Wu, MD,* Xiaoxi Dong, MD,† Chanjuan Chen, BS,* Wan Tang, BS,* Yujian Zhang, MD,* Mengxu Luo, BS,* Xianqin Wang, PhD,‖ Thomas J. Papadimos, MD, MPH,† and Xuzhong Xu, MD*

Table 1. Comparison of Pharmacokinetics Between the Lipid and Control Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lipid group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2α (min)</td>
<td>4 ± 1</td>
<td>2 ± 1</td>
<td>0.014</td>
</tr>
<tr>
<td>t1/2β (min)</td>
<td>110 ± 25</td>
<td>199 ± 38</td>
<td>0.001</td>
</tr>
<tr>
<td>Vd (L·kg⁻¹)</td>
<td>0.26 ± 0.05</td>
<td>0.24 ± 0.05</td>
<td>0.456</td>
</tr>
<tr>
<td>CL (mL·min⁻¹·kg⁻¹)</td>
<td>14 ± 4</td>
<td>9 ± 4</td>
<td>0.038</td>
</tr>
<tr>
<td>AUC (0–t) (mg·L⁻¹·min⁻¹)</td>
<td>588 ± 170</td>
<td>800 ± 371</td>
<td>0.233</td>
</tr>
<tr>
<td>AUC (0–∞) (mg·L⁻¹·min⁻¹)</td>
<td>640 ± 199</td>
<td>1123 ± 620</td>
<td>0.099</td>
</tr>
<tr>
<td>K10 (1/min)</td>
<td>0.05 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>0.111</td>
</tr>
<tr>
<td>K12 (1/min)</td>
<td>0.13 ± 0.04</td>
<td>0.32 ± 0.13</td>
<td>0.011</td>
</tr>
<tr>
<td>K21 (1/min)</td>
<td>0.02 ± 0.01</td>
<td>0.04 ± 0.03</td>
<td>0.170</td>
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</table>

The lipid sink effect and accelerated elimination play an important role in the distribution of bupivacaine in rats, both of which are important mechanisms of action of lipid emulsions in the reversal of the systemic toxicity of bupivacaine.
Effect of intravenous lipid emulsion on bupivacaine plasma concentration in humans

E. Litonius, P. Tarkkila, P. J. Neuvonen and P. H. Rosenberg

Bupi conc reduced by 111mcg/L at 20min and half-life reduced from 45min to 25min

No ‘lipid sink’ effect was observed with the non-toxic dose of bupivacaine used.”

Thus, the shortening of the bupivacaine context-sensitive half-life caused by lipid emulsion infusion seems to reflect that bupivacaine is distributed into tissues at an increased rate.

BUT

the hypothesised ‘lipid sink’ had little or no effect on the plasma disposition of the non-toxic concentration of bupivacaine in our study.
EXACTLY THE SAME, STRONG PK EFFECT IN RATS AND HUMAN VOLUNTEERS
DIFFERENT LABS, DIFFERENT CONTINENTS
DIFFERENT CONCLUSIONS
‘SORT OF’
A MORE FINE-GRAINED PK ANALYSIS
Multi-modal contributions to detoxification of acute pharmacotoxicity by a triglyceride micro-emulsion

Michael R. Fettiplace, Kinga Lis, Richard Ripper, Katarzyna Kowal, Adrian Pichurko, Dominic Vitello, Israel Rubinstein, David Schwartz, Belinda S. Akpa, Guy Weinberg

A
Recovery of carotid flow

B
Cardiac decay
Lipid modifies redistribution

A. Whole Blood

B. Whole Blood decay

C. Redistribution constants

D. Lipid: Plasma partition

Slope = 3.168 ± 0.2009
Lipid governs partitioning effect

A. In Vivo [Blood] vs [Heart]

B. [Plasma] vs [Cardiac]

C. In Silico [Blood] vs [Heart]

D. Partition Coefficient

Organ: Blood

Heart, Frontal Lobe, Cerebellum, Kidney, Lung
Mechanism: ACCELERATED REDISTRIBUTION

- Givers (heart and brain): conc goes down
- Receivers (skeletal muscle and liver): goes up
- Blood: WB up; plasma down

via

- Rapid transfer of bupivacaine
- Early, transient, fast shuttle
- Works best at highest bupivacaine concentrations

Requires a new view of lipid

LIPID IS A SHUTTLE, NOT A SINK!!!
Lipid Affects Intracellular Kinase Signaling Pathways

Insulin Signaling in Bupivacaine-induced Cardiac Toxicity

Sensitization during Recovery and Potentiation by Lipid Emulsion

Michael R. Fettiplace, M.S., Katarzyna Kowal, B.S., Richard Ripper, C.V.T., Alexandria Young, B.S., Kinga Lis, B.S., Israel Rubinstein, M.D., Marcelo Bonini, Ph.D., Richard Minshall, Ph.D., Guy Weinberg, M.D.

(Anesthesiology 2016; 124:428-42)
Typical initial lipid resuscitation bolus: 100mL of 20% = 20g fat

Total fat in a single serving of chicken soup: 27.2g
Controversies and Concerns

- Is there a Sink?
- Efficacy:
  - Enteral v Parenteral
- Safety
  - Dose v Overdose
  - Complications 2/2 lipid
- Best models
  - Stop pig experiments
Controversies and Concerns

• Is there a Sink?
• Efficacy:
  – Enteral v Parenteral
• Safety
  – Dose v Overdose
  – Complications 2/2 lipid
• Best models
  – Stop pig experiments
Controversies and Concerns

• Efficacy:
  – Enteral v Parenteral

• Safety
  – Dose v Overdose
  – Complications 2/2 lipid

• Best models
  – Stop pig experiments
Total dose delivered over 2 hours: 3L – 4L except for two patients

In our case series, ILE was used for different lipophilic drug intoxications to improve cardiovascular and neurologic symptoms. According to the results, it was found that ILE treatment is a lifesaving agent in lipophilic drug intoxications and it can be used in unconscious patients who have cardiac and/or neurologic symptoms but no history of a specific drug ingestion.
26yo multidrug overdose
Hypotension + bradycardia
unresponsive to volume, calcium, glucagon, high dose pressors.

ILE initiated
BP and HR Improved X 5 hours
CVVH attempted but
Unsuccessful due to high filtration pressures = filter obstruction
Blood very lipemic. Patient died.

Total dose: 6.2L = 79mL/kg
Safety of Lipid Infusion
Dixon ‘Up-Down’ Experiment

LD50 67.72 ± 10.7 mL/kg (n = 10).

NB: Average Dose in Case Reports 3.7mL/kg/30 minutes
D. Loading dose: 1.5 mL/kg bolus then,

Fast infusion: 0.25 mL/kg/min X 3 min then,

Slow infusion: ~0.025mL/kg/min X <6.5 hours

Goal = TG conc ~ 1%. 

Confusion About Infusion: Rational Volume Limits for Intravenous Lipid Emulsion During Treatment of Oral Overdoses

Michael R. Fettiplace, MS*; Belinda S. Akpa, PhD; Israel Rubinstein, MD; Guy Weinberg, MD

*Corresponding Author. E-mail: mfetti3@uic.edu, Twitter: @mfettiplace [Ann Emerg Med. 2015; 66(1): 1-4.]
Prolonged Use of Intravenous Lipid Emulsion in a Severe Tricyclic Antidepressant Overdose

Ravi Agarwala • Syed Zaki Ahmed • Timothy J. Wiegand

Case Report A patient with refractory cardiovascular collapse following an amitriptyline overdose was treated with ILE with initial improvement. Instability recurred after ILE discontinuation and lipid therapy was restarted, but high-dose treatment was complicated by severe lipemia. A low-dose infusion was instead used, and the patient did not experience further toxicity despite amitriptyline levels in the toxic range for 21 days. He survived to discharge without long-term sequelae.

Discussion A low-dose infusion of ILE was well tolerated and may have successfully prevented recurrent toxicity in a case of severe tricyclic antidepressant overdose.
Complications

(Volume Related)

- Lipemia – predictable
- Interference with laboratory values
- Volume overload
- Fat overload
- Weak evidence for association in other ADRs because of clinical confounders (drugs, shock):
  - Pancreatitis (chemical only; multiple confounders)
  - ARDS (multiple confounders)
"Adverse effects seem to be proportional to the rate of infusion as well as the total dose received".
Controversies and Concerns

• Efficacy:
  – Enteral v Parenteral

• Safety
  – Dose v Overdose
  – Complications 2/2 lipid

• Best models
  – Stop pig experiments
Hypersensitivity Reactions to Intravenous Lipid Emulsion in Swine: Relevance for Lipid Resuscitation Studies

Peter Bedocs, MD,* John Capacchione, MD,† Lauren Potts, MD,‡ Ryan Chugani,§ Zsoka Weiszhar, MSc,ǁ Janos Szebeni, MD, PhD, DSc,¶ and Chester C Buckenmaier, MD*

---

A

B

C

---

180 mmHg

0

70 mmHg

0

60 mmHg

0

lipid start
(5ml/kg)

lipid in

SAP

PAP

ETCO₂

---
Archie Cochrane

“Effectiveness and Efficiency: Random Reflections on Health Services”, 1971

The Father of Modern Statistical Medicine

David Sackett
METHODOLOGY

Methodology for AACT evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning

SOPHIE GOSSELIN,1 MARTIN MORRIS,2 ANDREA MILLER-NESBITT,2 ROBERT S. HOFFMAN,3 BRYAN D. HAYES,4 ALEXIS F. TURGEON,5 BRIAN M. GILFIX,6 AMI M. GRUNBAUM,6 THEODORE C. BANIA,7 SIMON H. L. THOMAS,8 JOSÉ A. MORAIS,9 ANDIS GRAUDINS,10 BENOIT BAILEY,11 BRUNO MÉGARBANE,12 DIANE P. CADELLO,13 MICHAEL LEVINE,14 SAMUEL J. STELLPFLUG,15 LOTTE C. G. HOEGBERG,16 RYAN CHUANG,17 CHRISTINE STORK,18 ASHISH BHALLA,19 CAROL J. ROLLINS,20 VALÉRY LAVERGNE,21 and ON BEHALF OF THE AACT LIPID EMULSION THERAPY WORKGROUP*

Then.....
Effects on non-LA toxicity
Effects on LA toxicity
Effects on laboratory analysis
Clinical adverse effects
ILE appears to be effective for reversal of cardiovascular or neurological features in some cases of LA toxicity but there is currently no convincing evidence showing ILE is more effective than vasopressors or to indicate which treatment should be instituted as first line therapy in severe LA toxicity". 
Double Reporting (and a pig study, too)

Subjective Assessment: ‘supports’ or doesn’t

De Queiroz et al. (2012) [88] (Pig)
- RCS; resuscitation model

Levobupivacaine (500 mg/h until symptoms)
- Survival: ILE 7/9, ILE + EPI 10/10, EPI 6/7, Control 1/7
- Yes

De Queiroz et al. (2014) [89] (Pig)
- RCS; resuscitation model

Levobupivacaine (8.3 mg/min)
- Yes; ILE, EPI, and ILE + EPI provided similar ROSC. ECG abnormalities from EPI or ILE + EPI increased compared to ILE
Lipid + Epinephrine: Paradox of Initial Recovery
- 'No support for therapeutic effect of ILE alone'
- 'All animals survived'
- 'No differences between epi and ILE mortality'
- 'Epi below 10mcg had more sustained ROSC'

Table 2. Animals Attaining Return of Spontaneous Circulation for Each Group and Time

<table>
<thead>
<tr>
<th></th>
<th>3 min</th>
<th>5 min</th>
<th>7.5 min</th>
<th>10 min</th>
<th>15 min</th>
</tr>
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<tbody>
<tr>
<td>Saline</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lipid control</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>5</td>
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<tr>
<td>1 mcg/kg</td>
<td>0</td>
<td>4</td>
<td>5</td>
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<tr>
<td>2.5 mcg/kg</td>
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<td>5</td>
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<td>4</td>
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<td>25 mcg/kg</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>3</td>
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</tbody>
</table>

n = 5 for all conditions.

- Survival reported as “All” despite this only being true for 1&2.5mcg/kg animals
- Average dose was 45mcg/kg; 94% received 10mcg/kg or more
- Saline ignored
Our best evidence: ‘No support for therapeutic effect of ILE alone’.

So, aggregate all the data from all (non-duplicative) studies, including pigs........
“….currently no convincing evidence showing ILE is more effective than vasopressors or to indicate which treatment should be instituted as first line therapy in severe LA toxicity”.

<table>
<thead>
<tr>
<th>Evidence Supports Lipid Resuscitation:</th>
<th>Mechanism</th>
<th>Efficacy</th>
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<tr>
<td>Lab</td>
<td>3 labs, ID same PK effect on LA: accelerated redistribution + Inotropic benefit: intact rat isolated heart</td>
<td>Intact animals (rats, dogs, rabbits, [pigs]). Isolated heart Cell culture In silico LA, CCB, TCA</td>
</tr>
<tr>
<td>Clinical</td>
<td>Volunteers X 2: PK effect no ADR</td>
<td>Case Reports Series Registry RCT (cats)</td>
</tr>
</tbody>
</table>
ADOPTION OF LIPID RESCUE IN LONDON HOSPITALS

Picard et al, Anaesthesia, 2009
Translation of laboratory findings to the clinical setting

... the first successful use of Lipid

Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest

Meg A. Rosenblatt, M.D.,* Mark Abel, M.D.,† Gregory W. Fischer, M.D.,† Chad J. Itzkovich, M.D.,‡ James B. Eisenkraft, M.D.§

INTERSCALENE BLOCK  20ml Bupivacaine 0.5% - 20ml Mepivacaine 1.5%
Within 30 sec seizures (Propofol 50+100mg); 90 sec later CARDIAC ARREST...
CPR,O2-ventilation,epinephrine,atropine,amiodarone,vasopressin, defibrillation...
PULSELESS VT... Within 15 sec OF LIPID pulse/blood pressure detectable

YES!!
Meg Rosenblatt saves the day
Yes, lipid works for LAST other than bupivacaine:

Intractable cardiac arrest due to lidocaine toxicity successfully resuscitated with lipid emulsion*

Stephanie K. Dix, MD; Gregg F. Rosner, MD; Monica Nayar, PharmD; Julian J. Harris, MD; Maya E. Guglin, MD; Jeffery R. Winterfield, MD; Zhiling Xiong, MD, PhD; Gilbert H. Mudge, Jr., MD

Use of Intravenous Lipid Emulsion to Reverse Central Nervous System Toxicity of an Iatrogenic Local Anesthetic Overdose in a Patient on Peritoneal Dialysis

D Bruce Lange, Daniel Schwartz, Gerald DaRoza, and Robert Gair

bolus (100 mL) over approximately 10 minutes. Within approximately 5 minutes (ie, after 50 mL of lipid was infused), the patient became more alert and exhibited improved muscle function. In approximately 10 minutes (after 100 mL), the patient was able to speak coherently and
Eyewitness account of (almost) fatal lidocaine toxicity
So, what will you do....
Conclusions

1. ILE is effective in specific settings
2. Enteral OD ≠ Parenteral OD
3. Don’t overdose!!

• Multimodal effects: scavenger + inotrope +...
• Role in parenteral OD best defined (LAST)
• Seeking optimal regime for oral OD
• Look to development of better agents
ACMT Position Statement: Guidance for the Use of Intravenous Lipid Emulsion

American College of Medical Toxicology

Recommended Guideline

Given the uncertainty of its beneficial effect in human poisonings, it is the opinion of the American College of Medical Toxicology that there are no standard of care requirements to use, or to choose not to use, ILE. However, in circumstances where there is serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, ILE is viewed as a reasonable consideration for therapy.
Intravenous models may not always apply to enteral overdose.

Intralipid Outperforms Sodium Bicarbonate in a Rabbit Model of Clomipramine Toxicity

Martyn Harvey, BHB, MBChB, FACEM
Grant Cave, BHB, MBChB, FACEM

From the Department of Emergency Medicine, Waikato Hospital, Hamilton, New Zealand (Harvey); and the Department of Intensive Care Medicine, Monash Medical Centre, Melbourne, Australia (Cave).

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
Clinical Experience with Intravenous Lipid Emulsion for Drug-Induced Cardiovascular Collapse

Ann-Jeannette Gelb · Erica Liebelt · Alex F. Manini ·
On behalf of the Toxicology Investigators' Consortium (Toxic)

N=9 (3 cardiac arrest, 6 refractory shock)
5 survived to discharge
Naranjo scores: lipemia, digit amputation, lung injury, renal failure, DVT
Misuse of the Naranjo Adverse Drug Reaction probability scale in toxicology

D. SEGER¹, K. BARKER², and C. McNAUGHTON³

Conclusion. Adverse events that occur in overdose patients are excluded from the definition of ADR. Yet in case reports or series of overdose patients, the Naranjo Scale has been applied to assess the probability an event was caused by the ingested drug or therapeutic modality. This application of the Naranjo Scale is not scientifically valid and may lead to erroneous conclusions. There is no evidence to support the application of the Naranjo scale to any events that occur in overdose patients.
Complications Following Antidotal Use of Intravenous Lipid Emulsion Therapy

Michael Levine • Aaron B. Skolnik • Anne-Michelle Ruha • Adam Bosak • Nathan Menke • Anthony F. Pizon

In this study, complications associated with ILE were relatively common. While it is impossible to definitively determine causality with this study design, given the temporal association and biologic plausibility, ILE is strongly implicated as the etiology of pancreatitis and laboratory interference.
Full Circle

CASE REPORT

Lipid resuscitation in a carnitine deficient child following intravascular migration of an epidural catheter

G. K. Wong, D. T. Joo and C. McDonnell

Assistant Professors and Staff Anesthesiologists, Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, University of Toronto, Ontario, Canada
Intravenous Lipid Emulsion given to Volunteers does not affect Symptoms of Lidocaine Brain Toxicity

Juho A. Heinonen¹, Erik Litonius¹², Tapani Salmi³, Juhani Haasio², Pekka Tarkkila², Janne T. Backman⁴
and Per H. Rosenberg¹

![Graph showing lidocaine base concentration over time](image)
Disclosure statement

All members completed a conflict of interest form for AACT and received no honoraria. Webcast conference and rooms for meeting were provided by AACT. No member with a financial or academic conflict of interest preventing neutral assessment of the literature participated in the review (i.e. no committee member’s livelihood or academic career is depending on a grant studying lipid emulsion in poisoning). Dr Lavergne and Dr Turgeon are recipients of salary support awards from the Fonds de la Recherche du Québec - Santé (FRQS).
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Healthy 53 year old man developed cardiogenic shock following bupivacaine-lidocaine regional anesthetic for elective outpatient shoulder surgery. Intubation, resuscitation, transfer to hospital. Profound biventricular dysfunction with normal coronary arteries. Placement of an intra-aortic balloon pump and intravenous vasoactive drugs, but the patient remained in shock. Stabilization was achieved with emergent cardiopulmonary bypass and temporary left ventricular assist device (LVAD). Twenty-four hours later, cardiac function normalized and the LVAD was removed. The patient was discharged five days later and remained with normal heart function in three-year follow-up.
“In previously reported cases of local anesthetic induced cardiovascular collapse, the successful use of an intravenous lipid infusion has been described [9,10]. However, these clinical reports presume a bupivacaine based toxicity, which may or may not have been the case reported here.”

“The cardiac dysfunction was global and persistent and was not a structural problem such as occult coronary arterial, valvular, or congenital disease. Rather, it appeared to be a profound chemical reaction that was not immediately reversible. “
Figure 9. Arterial pressure. Bar, 1 min. First arrow, cocaine 5 mg/kg; second arrow, lipid.

Figure 10. Continuous ECG. Each strip is 5 sec; arrow, lipid.
Simplest Demonstration Possible
Case reports of LAST over time
Then….and now