Lipid emulsion in clinical toxicology: appraisal of the evidence

Sophie Gosselin, MD, FRCPC, CSPQ, FAACT, FACMT
Chair, Lipid Emulsion in Poisoning workgroup

Associate Professor, Department of Medicine, McGill University
Centre Antipoison du Québec
Province of Alberta Drug Information Service

Madrid, May 27th 2016,
Disclosures

- I do not
  - own a patent
  - own shares in a company
  - have any grant pertaining to the use of lipid emulsion.

- I have strong academic bias for evidence-based medicine

- I am involved with a start up company doing online interactive teaching modules called “Montreal Medical Toxicology Initiative”.
Objectives

- Present the work of the Lipid Emulsion in poisoning workgroup
- Discuss the rationale for our recommendations on the use of lipid emulsions
Lipid emulsion workgroup
### Table 1. Workgroup participants.

<table>
<thead>
<tr>
<th>Name</th>
<th>Association</th>
<th>Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voting members</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sophie Gosselin, Canada</td>
<td>AACT</td>
<td>chair, emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Diane P. Calello, USA</td>
<td>AACT</td>
<td>pediatric emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Robert S. Hoffman, USA</td>
<td>AACT</td>
<td>emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Michael Levine, USA</td>
<td>AACT</td>
<td>emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Bryan D. Hayes, USA</td>
<td>AAPCC</td>
<td>pharmacist, clinical toxicologist</td>
</tr>
<tr>
<td>Christine Stork, USA</td>
<td>AAPCC</td>
<td>pharmacist, clinical toxicologist</td>
</tr>
<tr>
<td>Theodore C. Bania, USA</td>
<td>ACMT</td>
<td>emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Samuel J. Stellpflug, USA</td>
<td>ACMT</td>
<td>emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Ashish Bhalla, India</td>
<td>APAMT</td>
<td>internist, medical toxicologist</td>
</tr>
<tr>
<td>Andis Graudins, Australia</td>
<td>APAMT</td>
<td>emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Benoit Bailey, Canada</td>
<td>CAPCC</td>
<td>pediatric emergency physician, medical toxicologist</td>
</tr>
<tr>
<td>Ryan Chuang, Canada</td>
<td>CAPCC</td>
<td>medical toxicologist</td>
</tr>
<tr>
<td>Lotte C. G. Hoegberg, Denmark</td>
<td>EAPCCT</td>
<td>pharmacist, clinical toxicologist</td>
</tr>
<tr>
<td>Bruno Mégarbane, France</td>
<td>EAPCCT</td>
<td>critical care physician, medical toxicologist</td>
</tr>
<tr>
<td>Simon H. L. Thomas, UK</td>
<td>EAPCCT</td>
<td>internist, medical toxicologist</td>
</tr>
<tr>
<td>Sheldon Magder, Canada</td>
<td></td>
<td>cardiology, critical care physician, electrophysiologist, methodologist</td>
</tr>
<tr>
<td>Alexis F. Turgeon, Canada</td>
<td></td>
<td>anesthesiologist, critical care physician, epidemiologist, methodologist</td>
</tr>
<tr>
<td><strong>Non-voting members</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marjorie BonHommel, USA</td>
<td>CAMB</td>
<td>medical biochemist</td>
</tr>
<tr>
<td>Brian M. Gilfix, Canada</td>
<td>CAMB</td>
<td>medical biochemist</td>
</tr>
<tr>
<td>Ami M. Grunbaum, Canada</td>
<td>CAMB</td>
<td>medical biochemist</td>
</tr>
<tr>
<td>Valéry Lavergne, Canada</td>
<td>GRADE</td>
<td>epidemiologist, methodologist</td>
</tr>
<tr>
<td>José A. Morais, Canada</td>
<td>CGS &amp; ASN</td>
<td>internist, geriatrician, total parenteral nutrition specialist</td>
</tr>
<tr>
<td>Martin Morris, Canada</td>
<td></td>
<td>medical librarian</td>
</tr>
<tr>
<td>Andrea Nesbitt-Miller, Canada</td>
<td></td>
<td>medical librarian</td>
</tr>
<tr>
<td>Carol J. Rollins, USA</td>
<td>ASPEN</td>
<td>Pharmacist in nutritional support</td>
</tr>
</tbody>
</table>
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. CALELLO,13 MICHAEL LEVINE,14 SAMUEL J. STELPFLUG,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*
Methodology & Scope of work

- Defined PICO questions
- Gather the evidence needed
- Institute of Medicine ‘Guidelines we can trust’
- AGREE II checklist
- RAND/UCLA (Fitch & al. 2010)
- Members without conflict of interest
  - Representatives nominated by their association
  - Other experts in the field
Process

Gather the evidence

- Efficacy Local anaesthetics
- Efficacy non Local anaesthetics
- Adverse effects
- Analytical Interferences
- Costs & availability

Prepare voting statements

1. Identify clinical situations
2. Identify toxins
3. Iterative process keep/delete
4. Refine wording after 1st vote
5. External review associations
6. Final wording 2nd vote
Efficacy Local Anesthetic: systematic review

- Inception to December 2014; update 2015, no pre-treatment or in vitro
- 123 articles: 84 human (111 patients), 40 animal (1 had both)
- One RCT crossover with sub-toxic dose in 16 volunteers
  - no difference saline vs ILE
Clinical Toxicology, 2016
http://dx.doi.org/10.3109/15563650.2015.1126286

REVIEW

Systematic review of the effect of intravenous lipid emulsion therapy for non-local anesthetics toxicity

Michael Levine\textsuperscript{a}, Robert S. Hoffman\textsuperscript{b}, Valéry Lavergne\textsuperscript{c}, Christine M. Stork\textsuperscript{d}, Andis Graudins\textsuperscript{e}, Ryan Chuang\textsuperscript{f}, Samuel J. Stellpflug\textsuperscript{g}, Martin Morris\textsuperscript{h}, Andrea Miller-Nesbitt\textsuperscript{h}, Sophie Gosselin\textsuperscript{i} and for the Lipid Emulsion Workgroup*
Review of the effect of intravenous lipid emulsion on laboratory analyses

Ami M. Grunbaum, Brian M. Gilfix, Robert S. Hoffman, Valéry Lavergne, Martin Morris, Andrea Miller-Nesbitt, and Sophie Gosselin

Division of Medical Biochemistry, Department of Medicine, McGill University Health Centre, Montreal, Québec, Canada; Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, New York, USA; Department of Medical Biology, Sacré-Cœur Hospital, University of Montréal, Montréal, Québec, Canada; Schulich Library of Science and Engineering, McGill University, Montréal, Québec, Canada; Department of Emergency Medicine, McGill University Health Centre & Department of Medicine, McGill University, Montreal, Québec, Canada
Analytical interferences

Table 4. Summary of reported interferences for pharmaceuticals in serum due to exogenous lipids as reported by assay vendors.

<table>
<thead>
<tr>
<th>Analyte</th>
<th># Evaluations</th>
<th># Evaluations with interference</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen</td>
<td>2</td>
<td>1</td>
<td>[30,31]</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>2</td>
<td>0</td>
<td>[30,31]</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>1</td>
<td>0</td>
<td>[31]</td>
</tr>
<tr>
<td>digoxin</td>
<td>4</td>
<td>1</td>
<td>[30–32]</td>
</tr>
<tr>
<td>ethanol</td>
<td>2</td>
<td>0</td>
<td>[30,31]</td>
</tr>
<tr>
<td>gentamycin</td>
<td>2</td>
<td>1</td>
<td>[30,31]</td>
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<tr>
<td>lidocaine</td>
<td>1</td>
<td>1</td>
<td>[31]</td>
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<tr>
<td>lithium</td>
<td>2</td>
<td>0</td>
<td>[30,31]</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>1</td>
<td>0</td>
<td>[31]</td>
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<tr>
<td>phenytoin</td>
<td>2</td>
<td>1</td>
<td>[30,31]</td>
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<tr>
<td>procainamide</td>
<td>1</td>
<td>1</td>
<td>[31]</td>
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<tr>
<td>salicylate</td>
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<td>1</td>
<td>[30,31]</td>
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<tr>
<td>theophylline</td>
<td>3</td>
<td>1</td>
<td>[30–32]</td>
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<tr>
<td>tobramycin</td>
<td>2</td>
<td>0</td>
<td>[30,31]</td>
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<tr>
<td>valproate</td>
<td>2</td>
<td>0</td>
<td>[30,31]</td>
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<tr>
<td>vancomycin</td>
<td>2</td>
<td>0</td>
<td>[30,31]</td>
</tr>
</tbody>
</table>
### Analytical Interferences

**Table 5.** Interlaboratory variation with and without addition of lipid emulsion (14 mmol/L TG equivalent) (adapted from Brady, 1994) [15].

<table>
<thead>
<tr>
<th>Analyte</th>
<th>%CV without LE</th>
<th>%CV with LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>albumin</td>
<td>5%</td>
<td>13%</td>
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<tr>
<td>AST</td>
<td>15%</td>
<td>49%</td>
</tr>
<tr>
<td>bilirubin (total)</td>
<td>10%</td>
<td>105%</td>
</tr>
<tr>
<td>calcium</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>creatinine</td>
<td>7%</td>
<td>25%</td>
</tr>
<tr>
<td>glucose</td>
<td>5%</td>
<td>26%</td>
</tr>
<tr>
<td>iron</td>
<td>8%</td>
<td>55%</td>
</tr>
<tr>
<td>phosphate</td>
<td>6%</td>
<td>53%</td>
</tr>
<tr>
<td>total protein</td>
<td>4%</td>
<td>28%</td>
</tr>
<tr>
<td>urate</td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td>urea</td>
<td>5%</td>
<td>11%</td>
</tr>
</tbody>
</table>

aspartate transaminase (AST), coefficient of variation (CV), lipid emulsion (LE)
Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration

Bryan D. Hayes, Sophie Gosselin, Diane P. Calello, Nicholas Nacca, Carol J. Rollins, Daniel Abourbih, Martin Morris, Andrea Nesbitt-Miller, José A. Morais, and Valéry Lavergne, Lipid Emulsion Workgroup

Department of Pharmacy, University of Maryland Medical Center and Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, USA; Department of Medicine, McGill Faculty of Medicine, Emergency Medicine, McGill University Health Centre, Montréal, Canada; Province of Alberta Drug Information Services, Alberta, Canada; Antipoison du Québec, Québec, Canada; Medical Toxicology, Department of Emergency Medicine, Morristown Medical Center, Emergency Medical Associates, Morristown, NJ, USA; Department of Surgery, Division of Emergency Medicine, University of Vermont, Burlington, VT, USA; Banner-University Medical Center Tucson, University of Arizona College of Pharmacy, Tucson, AZ, USA; Department of Medicine, Division of Emergency Medicine, University of Toronto, Toronto, Canada; Life Sciences Library, McGill University, Montréal, Canada; Division of Geriatric Medicine, McGill University, Montréal, Québec, Canada; Department of Medical Biology, Sacré-Coeur Hospital, University of Montréal, Montréal, Canada
Clinical adverse events

- 36,933 citations; 114 articles (87 human studies; 27 animal studies)
- Organ dysfunction (cardiovascular, heme, AKI)
- Pulmonary effects (ARDS, ALI, hypoxia, V/Q mismatch)
- Hypersensitivity and allergic reactions
- Vascular occlusion (priapism, DVT, fat embolism; CVVHF/ ECMO clots)
- Infection susceptibility
- Fat overload: hypertriglyceridemia, lipemia, pancreatitis etc.
Clinical adverse events

- TPN cases with 500mL boluses that could mimic ILE overdose scenario
- ILE overdose cases
- Marked heterogeneity
  - Dose Bolus & infusion
  - Duration of treatment
- No apparent higher risk in elderly
- Neonates? pregnancy?
- Significant reporting and publication bias
Indications for ILE

Specific indications

Lipid emulsion is indicated in the treatment of XYZ toxicity:

a) In the presence of cardiac arrest, after Standard ACLS (CPR, airways) has been started

b) In the presence of LIFE-THREATENING toxicity
   - Lipid emulsion should be administered as first line therapy
   - Lipid emulsion be administered as part of treatment modalities
   - Lipid emulsion should be administered if other therapies fail (last resort)

c) In the presence of NON LIFE-THREATENING toxicity
   - Lipid emulsion should be administered as first line therapy
   - Lipid emulsion be administered as part of treatment modalities
   - Lipid emulsion should be administered if other therapies fail (last resort)
Putting it all together – Recommendations

- **GRADE methodology**

- Two 2 levels of **positive** or **negative** recommendations:
  - **Strong recommendation** = “we recommend or we do not recommend” = balance of expected desirable effects **clearly outweigh** the expected undesirable effects (taking into account quality of evidence, clinical efficacy, adverse effects/harms, costs/resources, values/preferences)
  - **Weak/conditional recommendation** = “we suggest or we do not suggest” = balance of expected desirable effects **probably outweigh** the expected undesirable effects

- **Neutral recommendation** = balance of expected desirable effects and undesirable effects **is closely balanced or uncertain**
Putting it all together – Voting statements

- Appropriateness of level of recommendation: Standard GRADE framework
- Clinical toxicology: “very low/low quality of evidence”
- Consensus-based process
- Measure the strength of the opinions within the group (median)
- Measure the dispersion of the opinions (upper or lower quartile)
- Measure any strong disagreement within the group (disagreement index)
- Transparency and robustness of the process
- Reduction of interpersonal influence (votes are anonymous).
Meaning of Individual votes

- **vote 9 or 8:** you think that the **benefits** of treating with ILE **greatly surpass** its **risks** and it should always be given in the described circumstances.

- **vote 7 or 6:** you think that the **benefits** of treating with ILE **surpass** its **risks** and it should generally be given in the described circumstances.

- **vote 5b:** you think that benefits of treating with ILE **is equivalent** to its risk (balance between risks vs benefits).

- **vote 5a:** you think that you **don’t have enough information** to provide an expert opinion on what is mostly beneficial between treating with ILE or not.

- **vote 4 or 3:** you think that the risks of treating with ILE surpass its benefits and that it should generally not be given in the described circumstances.

- **vote 2 or 1:** you think that the risks of treating with ILE greatly surpass its benefits and it should never be given in the described circumstances.
Disagreement Index

DI = IPR/ IPRAS

- IPRAS = IPRr + (AI * CFA),
- IPRAS = 2.35 + (AI * 1.5)
- AI = |5 – IPRCP|
- IPRCP is Central Point of IPR
  - Upper limit IPR + Lower limit IPR)/2

Definitions

- IPR = Interpercentile Range
- IPRAS is the IPR Adjusted for Symmetry required for disagreement
- IPRr is the Interpercentile Range required for disagreement when perfect symmetry exists (classically = 2.35);
- AI is the Asymmetry Index
- CFA is the Correction Factor for Asymmetry (classically = 1.5).
Recommendations

The workgroup votes on the statement on a 9-point Likert scale FOR (7-9) / NEUTRAL (4-6) / AGAINST (1-3)

- Median between 1-3 AND Disagreement index ≤ 1
  - Upper quartile between 1-3: Strong Recommendation = “We recommend...”
  - Upper quartile between 4-6: Weak Recommendation = “We suggest...”
- Median between 7-9 AND Disagreement index ≤ 1
  - Lower quartile between 7-9: Strong Recommendation = “We recommend...”
  - Lower quartile between 4-6: Weak Recommendation = “We suggest...”
- Median between 4-6 AND Disagreement index ≤ 1
  - Neutral Recommendation = “Balanced position or insufficient evidence”
- Disagreement index > 1
  - No Recommendation = “No agreement reached”

Research Recommendation

Not to give ILE...

to give ILE...
# Toxins

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td></td>
</tr>
<tr>
<td>All other local anaesthetics</td>
<td></td>
</tr>
<tr>
<td>Non-local anaesthetics</td>
<td></td>
</tr>
<tr>
<td>Antidysrhythmics Class 1</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
</tr>
<tr>
<td>Other tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td></td>
</tr>
<tr>
<td>Beta receptor antagonists (LS)</td>
<td></td>
</tr>
<tr>
<td>Beta receptor antagonists (NLS)</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
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<tr>
<td>Other antihistamines</td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td></td>
</tr>
<tr>
<td>Other insecticides</td>
<td></td>
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<tr>
<td>Lamotrigine</td>
<td></td>
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<tr>
<td>Malathion</td>
<td></td>
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<tr>
<td>Other pesticides</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Other antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Selective Serotonin Reuptake Inhibitors</td>
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</tr>
</tbody>
</table>
We recommend (1D)

- Bupivacaine
  - Cardiac arrest (1D)
  - In life threatening toxicity if other therapies fail (1D)
Indication of ILE in life-threatening toxicity with Bupivacaine: if other therapies fail (last resort)

Number of participants

Vote

AGAINST

FOR

MEDIAN = 8
Lower Quartile = 7
Disagreement Index = 0.2

1 1 2 3 4 5 6 7 8 9

0 5 10 15

FOR NEUTRAL AGAINST
We suggest (2D)

Life threatening toxicity

- **Bupivacaine**
  - As part of treatment modalities (2D)

- **Other local anaesthetics**
  - If other therapies fail (2D)

- **Amitriptyline**
  - If other therapies fail (2D)

- **Bupropion**
  - If other therapies fail (2D)
We recommend not to give

NON- Life threatening toxicity

- As 1\textsuperscript{st} line therapy
  - amitriptyline
  - diphenhydramine
We suggest not to give

Life threatening toxicity

- As 1st line therapy
  - amitriptyline
  - other TCA
  - non lipid soluble BB
  - bupropion
  - all CCB
  - cocaine
  - diphenhydramine
  - Insecticides
  - lamotrigine

- malathion
- pesticides
- antipsychotics
Indication of ILE in non-life-threatening toxicity with Amitriptyline: as first line therapy

Number of participants

Vote

1 2 3 4 5 6 7 8 9

AGAINST NEUTRAL FOR

MEDIAN = 1
Upper Quartile = 2
Disagreement Index = 0.1
We suggest not to give

NON-Life threatening toxicity

- **As 1\textsuperscript{st} line therapy**
  - ALL other toxins except local anaesthetics (neutral)
  - Other antihistamines (no recommendation)

- **As part of treatment modalities**
  - Amitriptyline, other TCA, lipid-soluble BB, dihydropyridines, cocaine, diphenhydramine, lamotrigine

- **If other therapies fail (last resort)**
  - Other TCA, dihydropyridines, diphenhydramine
Indication of ILE in life-threatening toxicity with non-lipid soluble betablockers: as first line therapy

Number of participants

Vote

1 2 3 4 5 6 7 8 9

AGAINST NEUTRAL FOR

MEDIAN = 2
Upper Quartile = 5
Disagreement Index = 0.5

D
Neutral: risk = benefits

- EVERYTHING ELSE (neutral risk = benefits)

- Other antihistamines (neutral we don’t have enough information)
Use of ILE in the treatment of Bupropion toxicity

MEDIAN = 6
Disagreement Index = 0.4

Number of participants

Vote

1 2 3 4 5 6 7 8 9

FOR NEUTRAL AGAINST

N
Indication of LET in non-life-threatening toxicity with other LA: as part of other treatment modalities

Number of participants

Vote

1 2 3 4 5 6 7 8 9

MEDIAN = 5
Disagreement Index = 0.98

N
No recommendation

- None
- Our disagreement index was all < 1.
Hypothetical scenario

Number of participants

Vote

Disagreement Index > 1

Nil
Hypothesised scenario

Disagreement Index > 1

Number of participants

Vote

0 1 2 3 4 5 6 7 8 9

AGAINST    NEUTRAL    FOR

Nil
Hypothetical scenario

Disagreement Index > 1

Number of participants

Vote

1 2 3 4 5 6 7 8 9

AGAINST  NEUTRAL  FOR

1  2  4  3  4  2

Nil
Dosing of ILE

Types of ILE
The type of ILE to be used is ...
- Intralipid® 10%
- **Intralipid® 20%**
- Intralipid® 30%
- ClinOleic® 20%
- Lipofundin® 20%
- Other

If using a bolus of ILE the dose of the bolus indicated is...
- 0.25 mL/kg
- 0.50 mL/kg
- 0.75 mL/kg
- 1.0 mL/kg
- 1.25 mL/kg
- 1.5 mL/kg
- 1.75 mL/kg
- 2.0 mL/kg

If using an infusion of ILE the dose of the infusion indicated is...
- 0.25 mL/kg/min
- 0.5 mL/kg/min
- 0.75 mL/kg/min
- 1.0 mL/kg/min
- Other
Formulation of ILE to be used with Bupivacaine

MEDIAN = 7
Lower Quartile = 5
Disagreement Index = 0.4
Cessation of ILE

The decision to terminate the ILE treatment is indicated based on...

- Total (maximum) duration of the infusion regardless of dose or clinical improvement
- Total (maximum) dose administered regardless of duration of infusion or clinical improvement
- Clinical improvement regardless of dose or duration administered
- Other

In considering the total duration of the infusion as a criterion, lipid emulsion cessation is indicated, regardless of other factors such as clinical improvement or dose after...

10-20 min
21-30 min
31-40 min
41-50 min
51-60 min
Other
Cessation of ILE

In considering the maximum dose of lipid emulsion administered as a criterion, lipid emulsion cessation is indicated, regardless of clinical improvement or duration after...

- 8 mL/kg or less
- 8.1-10.0 mL/kg
- 10.1-12.0 mL/kg
- 12.1-14.0 mL/kg
- 14.1-16.0 mL/kg
- 16.1-18.0 mL/kg
- 18.1-20.0 mL/kg
- Other

In considering the clinical improvement as a criterion, lipid emulsion cessation is indicated, regardless of dose or duration after...

- As soon as symptoms resolution occurred
- After resolution of symptoms for 15-30 min
- After resolution of symptoms for 31-45 min
- After resolution of symptoms for 46-60 min
- Other
Clinical Toxicology community duty

- Provide advice on best available science
- Be devoid of commercial bias
- Advocate for safe use of therapies
Clinical Toxicology community duty

- The message received by many in the Em and critical care community

- Lipids are *proven to be useful* for all kinds of overdose

- Lipids have no adverse effects

- The more the better

- The earlier the better
Questions requiring **clinical data**

- Does it work at all?
- Which substances, which route of exposure?
- Is it better than other therapies with known adverse effect profile?
- What is the optimal dose of lipid emulsion?
- What is the optimal timing of lipid emulsion?
- What is the effect of ILE on other resuscitative medications?
Personal acknowledgement

- Lotte Høgberg
- Valéry Lavergne
- Bob Hoffman
- Michael Levine
- Bryan Hayes
- Ami Grunbaum
- Karen Simone & Alex Campbell
- Michael Mullins
- Martin Caravati
- Marc Ghannoum
- Daniel Morris & Jakob Stensballe
  - aka the lipid widowers
## Local anesthetic efficacy systematic review

### Animal randomized experiments: multiple arms n=29

<table>
<thead>
<tr>
<th>N</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>ILE vs EPI</td>
<td>ILE &gt; ILE in 4/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ILE &gt; Epi+ vaso in 1/9</td>
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<tr>
<td></td>
<td></td>
<td>ILE = Epi in 5/9</td>
</tr>
<tr>
<td></td>
<td>ILE + EPI vs ILE/EPI</td>
<td>ILE + EPI &gt; ILE alone in 6/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ILE + EPI = EPI alone in 2/8</td>
</tr>
<tr>
<td>19</td>
<td>ILE vs crystalloids</td>
<td>ILE &gt; saline in 10/19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ILE = saline in 6/19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Groups different in 1/19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear in 2/19</td>
</tr>
<tr>
<td>5</td>
<td>ILE vs ILE</td>
<td>Different formulation 20% vs 30%</td>
</tr>
</tbody>
</table>
## Human data

<table>
<thead>
<tr>
<th>RCT *unpublished</th>
<th>16 healthy volunteers</th>
<th>8 mg/min ropivacaine/levobupivacaine ILE 20% 120 mL or NS Time to induce early neurotoxicity no difference but indirectness; uncertain generalizability to overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports N=73+7 Case series n=2 (patients)</td>
<td>ILE beneficial n= 59 (71%) ILE no benefit n = 4 (5%) Unclear n = 10 (12%) Unreported n=10 (12%)</td>
<td>ILE 20% n= 76 ILE bolus n= 30 ILE bolus + infusion n =24 ILE infusion n=8 Vasopressors n=29 Sodium bicarbonate n=7 Other treatments not reported n=9</td>
</tr>
</tbody>
</table>