Lipid emulsions in the treatment of acute poisoning: a mini-review of human and animal studies

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Introduction

- Each year, more than a thousand deaths caused by poisonings are reported to American poison control centers.

- The most commonly involved substances include:
  - analgesics,
  - sedative/hypnotics
  - Antipsychotics
  - antidepressants
  - stimulants
  - street drugs
  - cardiovascular drugs
  - Poison (O.P., O.chlo, Carbamats,....).

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**history:**

- The discovery that an infusion of lipids may aid in the resuscitation of a patient in cardiac arrest due to LA toxicity was an incidental, serendipitous finding by Weinberg et al.
- In 1998 Dr. Weinberg began working on the metabolic effects of local anesthetics and discovered that an infusion of lipid emulsion could protect against and correct local anesthetic cardiac toxicity.
- The group sought to confirm the accidental observation by pretreating rats with an infusion of lipids and then measuring the dose of bupivacaine required to induce asystole.
- Indeed, rats that had been pretreated with a lipid infusion were able to withstand greater doses of bupivacaine before experiencing asystole.

(Weinberg GL, Pretreatment or resuscitation with a lipid infusion shifts the L. Anesthesiology. 1998;88(4):1071-1075)
ILE in the treatment of acute poisoning:
a mini-review of human and animal studies.

**History:**

- **other animal studies**
- The first successful clinical application of lipid rescue following systemic local anesthetic toxicity was reported in 2006, Dr. Hoffman.
- Dr. Meg A. Rosenblatt and her colleagues in the anesthesiology department of Mount Sinai School of Medicine, New York, used a 20% lipid emulsion to resuscitate a patient in prolonged bupivacaine-related cardiac arrest. The patient recovered with no neurologic sequelae after more than 20 minutes of asystole and nonresponse to advanced cardiac life support (Anesthesiology 2006;105:217-8).
- **In local anesthesia**
ILE in the treatment of acute poisoning:
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History:

Welcome

LipidRescue™ resuscitation refers to the use of an intravascular infusion of a lipid emulsion to treat severe, systemic drug toxicity or poisoning. It was originally developed to treat local anesthetic toxicity, a potentially fatal complication of regional anesthesia that can also occur in other situations where patients receive local anesthetic injections. More recently, LipidRescue has been proposed (in articles in the ER literature and elsewhere) as a treatment modality for poisoning or overdose by lipophilic agents in general. Support for this view is provided...
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The Association of Anaesthetists
of Great Britain & Ireland

Guidelines for the Management of Severe Local Anaesthetic Toxicity

**Signs of severe toxicity:**

- Sudden 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 the initial injection

**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 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

**Management of cardiac arrest associated with LA injection:**

- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that they may be very refractory to treatment
- Prolonged resuscitation may be necessary; it may be appropriate to consider other options:
  - Consider the use of cardiopulmonary bypass if available
  - Consider treatment with lipid emulsion

**Treatment of cardiac arrest with lipid emulsion:** (approximate doses are given in red for a 70-kg patient)

- Give an intravenous bolus injection of Intralipid® 20% 1.5 ml.kg⁻¹ over 1 min
  - Give a bolus of 100 ml
- Continue CPR
- Start an intravenous infusion of Intralipid® 20% at 0.25 ml.kg⁻¹.min⁻¹
  - Give at a rate of 400 ml over 20 min
- Repeat the bolus injection twice at 5 min intervals if an adequate circulation has not been restored
  - Give two further boluses of 100 ml at 5 min intervals
- After another 5 min, increase the rate to 0.5 ml.kg⁻¹.min⁻¹ if an adequate circulation has not been restored
  - Give at a rate of 400 ml over 10 min
- Continue infusion until a stable and adequate circulation has been restored

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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

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• **Local anesthetics**

In a model of bupivacaine-induced cardiac arrest, IFE resulted in a 100% survival in dogs compared to Placebo

In their experiment, a toxic dose of bupivacaine was administered intravenously to 12 dogs under isoflurane general anesthesia. After the development of asystole, all dogs received internal cardiac massage for 10 minutes.


- **Local anesthetics**

  There was 100% return in spontaneous circulation in pigs treated with an epinephrine/vasopressin combination and none in those who received IFE.

• **Local anesthetics**

There was a 30% increase in bupivacaine LD50 following IFE administration in one study in rats

• Median cumulative bupivacaine LD (mg/kg)
  • NS 17.8 versus IL10 27.6 versus IL20 49.8 versus IL30 82.0,  \( p < 0.001 \) between all groups.

• (Weinberg G, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwick M.J. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Anesthesiology 1998; 88(4):1071-1075.)
• **Other substances**

  • IFE decreased mortality from clomipramine toxicity by 80% when compared to placebo.


- **Other substances**
  - In models of verapamil toxicity, IFE increased time required to kill all animals when compared to normal saline.
  - IFE almost doubled the LD50 in rats..

### Other substances

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subject (total)</th>
<th>Drug (iv route unless specified)</th>
<th>Treatment evaluated</th>
<th>Timing of IFE infusion</th>
<th>Length of follow-up of subjects</th>
<th>Outcomes measured at the end of follow-up (unless specified)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teb-but (2006)</td>
<td>Rats (30)</td>
<td>Verapamil 37.5 mg/kg/h</td>
<td>1. IL 20% 12.4 mL/kg, over 5 min 2. NS 0.9% 12.4 mL/kg</td>
<td>5 min post-intoxication</td>
<td>Until death of all rats</td>
<td>Survival time (min)</td>
<td>NS 24 ± 9 versus IL 44 ± 21, p = 0.003</td>
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<td></td>
<td>Verapamil LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</td>
<td>NS 13.6 (CI 12.2–15.0) versus IL 25.7 (CI 24.7–26.7)</td>
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<td>Rate of drop in HR (beats per min)</td>
<td>NS 6.8 (CI 8.3–5.2) versus IL 10.7 (CI 12.6–8.9)</td>
</tr>
<tr>
<td>Ban-ia (2007)</td>
<td>Dogs (14)</td>
<td>Verapamil 6 mg/kg/h (until 50% MAP drop) then 2 mg/kg/h</td>
<td>1. IFE 20% 7 mL/kg, over 30 min 2. NS 0.9% same volume of verapamil</td>
<td>45 min after the beginning of verapamil</td>
<td>120 min</td>
<td>Survival rate at 120 min (%)</td>
<td>NS 14 versus IL 100, p = 0.01</td>
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<td>Mean survival time (min)</td>
<td>NS 75 versus IL greater than 120, p = 0.002</td>
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<td>MAP difference at 60 min between group (CI in mmHg)</td>
<td>NS 10.2–53.1 lower than IL, p &lt; 0.05</td>
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<td></td>
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<td></td>
<td>HR at 60 min</td>
<td>NS = IL *</td>
</tr>
</tbody>
</table>

- **Other substances**

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<thead>
<tr>
<th>Trial</th>
<th>Subject (total)</th>
<th>Drug (iv route unless specified)</th>
<th>Treatment evaluated</th>
<th>Timing of IFE infusion</th>
<th>Length of follow-up of subjects</th>
<th>Outcomes measured at the end of follow-up unless specified (units of measure)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez (2008)</td>
<td>Rats (30)</td>
<td>Verapamil 15 mg/kg/h</td>
<td>All antidotes were IFE boluses 1. 0 mL/kg (IL0) 2. 6.2 mL/kg (IL6) 3. 12.4 mL/kg (IL12) 4. 18.6 mL/kg (IL18) 5. 24.8 mL/kg (IL24) 6. 37.6 mL/kg (IL37)</td>
<td>5 min after beginning of verapamil infusion</td>
<td>Until death</td>
<td>Mean survival time (min)</td>
<td>ILO 34 versus IL6 58 versus IL12 63 versus IL18 144 versus IL24 126 versus IL37 130, $p = ?$</td>
</tr>
<tr>
<td>Medlej (2008)</td>
<td>Rats (14)</td>
<td>Verapamil 15 mg/kg/h</td>
<td>1. IFE 20% 18.6 mL/kg over 30 min 2. NS 0.9% same volume</td>
<td>Pretreatment 2 h prior verapamil infusion</td>
<td>Until death</td>
<td>Survival time (min)</td>
<td>NS 39 (CI 31–47) versus IFE 53 (CI 43–63), $p = 0.03$</td>
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<td>MAP (mmHg)</td>
<td>NS $\approx$ IFE at all time*</td>
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<td></td>
<td>HR (beats per min)</td>
<td>NS lower than IFE by 53 (CI 0.8–105) at 30 min NS $\approx$ IFE at any other time*</td>
</tr>
</tbody>
</table>
• **Other substances**

• No mortality benefit from IFE over placebo was observed in a model of nifedipine toxicity.

• **Other substances**
  
  • IFE did not affect mortality in a rat model of propranolol toxicity when compared to placebo.

• **Case reports**

• Local anesthetics

• Successful return of spontaneous circulation attributed to IFE administered after cardiac arrest because of local anesthetic intoxication was reported in 23 unpublished (www.lipidresque) and 16 published case reports.

- **Case reports**
- **Local anesthetics**

**In 2006, Dr. Rainer J. Litz and his colleagues at University Hospital Dresden, Germany, reported on the rescue of an 84-year-old woman in asystolic cardiac arrest secondary to the accidental overdose of**

**After 10 minutes of unsuccessful cardiopulmonary resuscitation, they administered a bolus of 100 mL of 20% lipid emulsion followed by a continuous infusion of 10 mL per minute. After a total IFE dose of 200 mL, spontaneous electrical activity resumed and cardiac output was restored. "The patient recovered fully," (Anaesthesia 2006;61:800-1).**

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- **Case reports**
  - Other substances

- **Dr. Archie J. Sirianni** and his colleagues at Riddle Memorial Hospital in Media, Pa., reported the use of IFE in a 17-year-old girl who developed seizures and cardiovascular collapse after intentionally ingesting an overdose of bupropion, lamotrigine and amphetamine.

- Following 70 minutes of unsuccessful standard cardiopulmonary resuscitation, a 100-mL IV bolus of 20% lipid emulsion was administered, followed by an effective sustained pulse 1 minute later and subsequent improvement in cardiovascular status and recovery with near-normal neurologic function.


- **Case reports**
- Other substances

In an unpublished case report of calcium channel blocker overdose not proven by serum analysis, return of spontaneous circulation leading to **full neurological recovery** was achieved within 5 min of IFE administration in a patient in **cardiac arrest** for 80 min. ([www.lipidrescue](http://www.lipidrescue))

- **Case reports**
- **Other substances**

A 45-year-old woman came to the hospital reporting palpitations and chest pain and toxicology screening was positive for cannabis. She was given haloperidol, 5 mg, by rapid intravenous injection for her agitation, and within minutes, she developed ventricular bigeminy followed by pulseless, multiform ventricular tachycardia. Cardiopulmonary resuscitation was initiated, and the patient underwent tracheal intubation and was given 4 counter shocks, intravenous epinephrine, atropine, and amiodarone, without restoration of normal rhythm. Thirteen minutes after the current patient’s arrest, we gave her 250 mL of 20% lipid emulsion intravenously. Within 2 minutes, her rhythm converted to a narrow, supraventricular tachycardia with a palpable pulse. Five minutes later, blood pressure was 100/60 mm Hg, and the patient sat up and required physical restraint and sedation with diazepam and propofol.

- Weinberg, Guy. 2009. Reversal of Haloperidol-Induced Cardiac Arrest by Using Lipid Emulsion. Annals of Internal Medicine, 150, 737-8

- **Local anesthetics**

  When compared to epinephrine, vasopressin, or both combined, IFE increases the rate-pressure product (heart rate x systolic pressure) of rats in bupivacaine induced cardiac arrest.

  Also, IFE increases the heart rate in animal models of bupivacaine toxicity when compared to placebo, to vasopressin, or to the combination of vasopressin and epinephrine.

• **Other substances**

- IFE appears to consistently increase the mean arterial pressure in animal models of propranolol, verapamil, and clomipramine toxicity when compared to placebo and in a model of clomipramine toxicity when compared to bicarbonate.

- No effect on mean arterial pressure was noted in models of amitriptyline and atenolol toxicity.

- Heart rate changes were inconsistent among trials that studied verapamil.

• Case reports
• Local anesthetics

Following administration of IFE, normalization of heart rates and blood pressures was noted in nine case reports of hypotension or hypertension secondary to local anesthetic toxicity.

• Other substances.

Normalization of hypotension or bradycardia with IFE was reported in one human case report of suspected ingestion of atenolol, one of verapamil, one of possible co-ingestion of verapamil and atenolol, and one of imipramine overdose.

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• **Case reports /Other substances.**
  
  A 27-year-old male was found unresponsive at a subway station--> He promptly had two generalized tonic–clonic seizures, each lasting 10 s,-->He developed pulseless ventricular tachycardia (VT) and received CPR as well as IV boluses of epinephrine and NaHCO₃. Return of spontaneous circulation (ROSC) occurred after 18 min, and an infusion of epinephrine was started at 20μg/min.--->The patient was transferred to the ICU at 0605 h and despite a narrow complex ECG he required high dose infusions of epinephrine (up to 20 μg/min) and norepinephrine (up to 80 μg/min) to maintain his mean arterial pressure >65 mmHg. --> An initial bolus of 100mL of 20% Intralipid (Baxter Corporation, Canada) was given (estimated patient weight of 80 kg) followed by an infusion of 400mL over 30 min. The doses of norepinephrine and epinephrine infusions were rapidly weaned and eventually discontinued at 1500 h (Fig. 1).-->The patient was extubated the next morning. The following day the patient had a GCS of 15 and was discharged from the ICU. His urine toxicology screen returned positive for tricyclic antidepressants.

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- Paul T. Engels, 2010: Intravenous fat emulsion to reverse haemodynamic instability from intentional amitriptyline overdose, Resuscitation, 81, 1037-1039

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- **Local anesthetics**
  - IFE decreased the QRS duration in animal models of bupivacaine toxicity


  - IFE and Epin return to baseline values by 5 min,

  - Epin ≈ IFE after 5 min

  - NS > IFE ($d = 3.87$, $p < 0.05$),

  - NS > Epin ($d = 2.88$, $p < 0.05$) at 10 min

**Other substances**

♠ IFE decreased QRS duration in an animal model of propanolol toxicity.

♠ However, no effect could be found with clomipramine.


• **Case reports**
• **Local anesthetics**

• In case reports involving local anesthetics, IFE played a role in decreasing QRS width, stopping extrasystoles, and converting asystole, torsades de pointes, and ventricular fibrillation into a perfusing rhythm

> 10 cases
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a mini-review of human and animal studies.

- **Case reports**
- **Other substances**

→ In a case report of bupropion, lamotrigine, and amphetamine overdose, QRS narrowing occurred over 15 min following IFE administration.

→ and 4 h later in case of suspected amitriptyline intoxication.

→ IFE decreased the frequency of recurrent ventricular arrhythmia in a case of suspected imipramine overdose.

- **Local anesthetics**
  - IFE shortens rats’ thiopental anesthesia time
  - IFE unexpectedly reversed the deep coma of a dog presumably intoxicated with avermectin (www.lipidresque)
• **Case reports**

• **Other substances**

- IFE did not improve the comatose state of a patient with presumed *mirtazapine* and *quetiapine* overdose.

- A published case report parallels the gradual resolution of a comatose state in a patient with suspected quetiapine, sertraline, and benzodiazepine overdose.

- Seizures were aborted in a patient with a TCA toxidrome.

- A comatose patient with suspected verapamil and atenolol intoxication awakened within minutes of IFE therapy.

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ABSTRACTS

Abstracts of the 2009 North American Congress of Clinical Toxicology Annual Meeting, September 21–26, 2009, San Antonio, Texas, USA

A 16 year-old girl with bipolar disorder and recent gastrotomy for battery ingestion was transferred to the intensive care unit from the psychiatric ward after ingesting **38 tablets of quetiapine 300 mg**, Other medications included **lamotrigine** and **lithium (Li+)**.

- **Hypotensive (70/30), tachycardic (150s), and stuporous, responding only to deep painful stimuli with incomprehensible sounds,**

**EKG:** Sinus at 127 bpm, QRS 92ms, and **QTc of 610ms** (baseline 462ms).

Due to mental status depression, hypotension, and extremely prolonged QTc with concern for degeneration of cardiac rhythm, intralipid was administered.

- A **one hundred milliliter (mL) bolus of a 20% lipid emulsion** was given intravenously over 5 minutes, followed by a **420 mL infusion over one hour**.

  - **Within one half hour**, the QTc interval narrowed to 433ms.
  - **Her GCS improved from 7 to 10** shortly after the infusion and then to 12 a few hours later. Eleven hours after her ingestion, she was alert and speaking clearly.
Intralipid reverses coma associated with zopiclone and venlafaxine overdose
Sam G. Hillyard, Casiano Barrera-Groba and Ruth Tighe
From the Department of Anaesthesia and Intensive Care Medicine, Royal Sussex County Hospital, Brighton, UK

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A 55-year-old man was brought into hospital by ambulance with a reduced level of consciousness.---> overdose of zopiclone and the sustained release formulation of venlafaxine (1.8 g of venlafaxine and an unknown quantity of zopiclone prior to admission) ---Glasgow coma score (GCS) was 10

---Four hours later, as there had been a decline in his GCS to 3.--- give Intralipid, which had recently been reported to reverse the coma generated by similarly lipophilic drugs.----> 100 ml (1.5 ml kg\(^{-1}\)) bolus of Intralipid, followed by a 400 ml infusion over the next 40 min.---- > Over the course of 30 min, his GCS improved to 11, negating the need for airway management. -->for 3 h after completing the ILE. His GCS had increased to and remained at 14. --- He was discharged from hospital 2 days later following psychiatric review.
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Dose it use only as an anti-cardiotoxic antidote?

One patient was in full cardiac arrest and asystolic from bupivacaine. All others were unstable with seizures and hypotension. In all cases, clinical improvement occurred within a few minutes of lipid emulsion administration. One patient had rapid resolution of seizures and hypotension from flecanide, but received lipid emulsion late in the course of toxicity and failed to recover.


- There aren’t any clinical trial (neither single nor double blind)

- Only case report and case series

**Intralipid® 20%**

A 20% I.V. Fat Emulsion
In Excel® Container

**What is intralipid?**

**MADE UP OF 20% SOYBEAN OIL, 1.2% EGG YOLK PHOSPHOLIPIDS, 2.25% GLYCERIN, AND WATER FOR INJECTION.**

IN ADDITION, SODIUM HYDROXIDE HAS BEEN ADDED TO ADJUST THE PH SO THAT THE FINAL PRODUCT PH IS 8. PH RANGE IS 6 TO 8.9

The major component fatty acids are linoleic (44-62%), oleic (19-30%), palmitic (7-14%), linolenic (4-11%) and stearic (1.4-5.5%)

### DESCRIPTION
Sterile fat emulsions for intravenous infusion containing:

<table>
<thead>
<tr>
<th>Content</th>
<th>Intralipid 10%</th>
<th>Intralipid 20%</th>
<th>Intralipid 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soya oil</td>
<td>100 g</td>
<td>200 g</td>
<td>300 g</td>
</tr>
<tr>
<td>Egg lecithin</td>
<td>12 g</td>
<td>12 g</td>
<td>12 g</td>
</tr>
<tr>
<td>Glycerol</td>
<td>22.0 g</td>
<td>22.0 g</td>
<td>16.7 g</td>
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<tr>
<td>Sodium hydroxide</td>
<td>to pH 6.0-9.0</td>
<td>to pH 6.0-9.0</td>
<td>to pH 6.0-9.0</td>
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<tr>
<td>Water for injections</td>
<td>to 1000 mL</td>
<td>to 1000 mL</td>
<td>to 1000 mL</td>
</tr>
<tr>
<td>Osmolality (mOsmol/kg water)</td>
<td>300</td>
<td>350</td>
<td>310</td>
</tr>
<tr>
<td>Energy content</td>
<td>1100 (4600)</td>
<td>2000 (8400)</td>
<td>3000 (12600)</td>
</tr>
</tbody>
</table>

- Clearance of the fat particles in IVFEs is mediated by the enzyme lipoprotein lipase. Adverse effects are more likely if the rate or duration of IVFE administration exceeds the enzyme's clearance capacity.

- AEs are also more likely after administration of a 10% IVFE formulation than a 20% formulation, because the higher concentration of free phospholipid in the 10% formulation interferes with lipoprotein lipase activity.

- Recent clinical trials involving clevidipine, which is formulated in a 20% IVFE, have demonstrated a low rate of lipid-related AEs.


- rat → Bupivacaine 0.75% 10 mL/kg/min until 10 s of asystole

1. IL 10%
2. IL 20%
3. IL 30%
4. NS 0.9%

Same infusion in each group: 3 mL/kg/min for 5 min

Median cumulative bupivacaine LD (mg/kg)
- NS 17.8
- IL10% 27.6
- IL20% 49.8
- IL30% 82.0

p < 0.001 between all groups


which dosage is better?

• Animal Dosage

The most study: 6 or 8 ml/kg 20% Intralipid, over a 4-minute period

BUT:

Basic Investigation

Determining the Optimal Dose of Intravenous Fat Emulsion for the Treatment of Severe Verapamil Toxicity in a Rodent Model

Eric Perez, MD, Theodore C. Bania, MD, Kamal Medlej, MD, Jason Chu, MD

Basic Investigation

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**Figure 2.** Mean survival.

**Figure 3.** Mean arterial pressure (MAP) at 60 minutes. IFE = intravenous fat emulsion. Note: Whiskers are 95% confidence intervals (CIs). This graph does not contain data from animals that expired before the 60-minute mark.

Basic Investigation

Determining the Optimal Dose of Intravenous Fat Emulsion for the Treatment of Severe Verapamil Toxicity in a Rodent Model

Eric Perez, MD, Theodore C. Bania, MD, Kamal Medlej, MD, Jason Chu, MD

CONCLUSIONS

IFEs improve survival, HR, MAP, and ABE in severe verapamil toxicity in a rodent model. The greatest benefit to survival occurs with 18.6 mL/kg IFE, while the greatest benefit to HR, MAP, and BE occurs at 24.8 mL/kg IFE. We believe 18.6 mL/kg IFE to be the optimal dose for the treatment of severe verapamil toxicity in this rodent model.
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- rat $\rightarrow$ Verapamile 15 mg/kg/h $\rightarrow$

IFE 18.6 mL/kg over
1. 15 min
2. 30 min
3. 45 min
4. 60 min

Increase Mean survival time (min)
1.9 (CI 0.16–3.6) for every minute of faster infusion, $p = 0.034$


• **Human Dosage**

The Association of Anaesthetists of Great Britain & Ireland

Guidelines for the Management of Severe Local Anaesthetic Toxicity

**Treatment of cardiac arrest with lipid emulsion:** (approximate doses are given in red for a 70-kg patient)

- Give an intravenous bolus injection of Intralipid® 20% 1.5 ml.kg⁻¹ over 1 min
  - Give a bolus of 100 ml
- Continue CPR
- Start an intravenous infusion of Intralipid® 20% at 0.25 ml.kg⁻¹.min⁻¹
  - Give at a rate of 400 ml over 20 min
- Repeat the bolus injection twice at 5 min intervals if an adequate circulation has not been restored
  - Give two further boluses of 100 ml at 5 min intervals
- After another 5 min, increase the rate to 0.5 ml.kg⁻¹.min⁻¹ if an adequate circulation has not been restored
  - Give at a rate of 400 ml over 10 min
- Continue infusion until a stable and adequate circulation has been restored

Moshiri M. Etamad L..

AAGBI Safety Guideline
Management of Severe Local Anaesthetic Toxicity

IMMEDIATELY

Give an initial intravenous bolus injection of 20% lipid emulsion 1.5 ml.kg⁻¹ over 1 min
AND
Start an intravenous infusion of 20% lipid emulsion at 15 ml.kg⁻¹.h⁻¹

AFTER 5 MIN

Give a maximum of two repeat boluses (same dose) if:
- cardiovascular stability has not been restored or
- an adequate circulation deteriorates
Leave 5 min between boluses
A maximum of three boluses can be given (including the initial bolus)
AND
Continue infusion at same rate, but:
Double the rate to 30 ml.kg⁻¹.h⁻¹ at any time after 5 min, if:
- cardiovascular stability has not been restored or
- an adequate circulation deteriorates
Continue infusion until stable and adequate circulation restored or maximum dose of lipid emulsion given

Do not exceed a maximum cumulative dose of 12 ml.kg⁻¹

**Human Dosage**

An approximate dose regimen for a 70-kg patient would be as follows:

**IMMEDIATELY**

- Give an initial intravenous bolus injection of 20% lipid emulsion 100 ml over 1 min
- Start an intravenous infusion of 20% lipid emulsion at 1000 ml.h⁻¹

**AFTER 5 MIN**

- Give a maximum of two repeat boluses of 100 ml
- Continue infusion at same rate but double rate to 2000 ml.h⁻¹ if indicated at any time

_Do not exceed a maximum cumulative dose of 840 ml_

Moshiri M. Etamad L.

• **Human Dosage**

• A protocol was describing a bolus of 1.5mL/kg 20% intralipid,

• followed by a 0.25mL/kg/min infusion to a max of 25 min or 8mL/kg.

On which medications are working?
<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Human report</th>
<th>Animal study</th>
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<tbody>
<tr>
<td>Local Anesthesia</td>
<td>Bupivacaine</td>
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<td>Antidepressant</td>
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<td>Clomipramine</td>
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<td>Others</td>
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<td>Ca Chanal Blockers</td>
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<td>Nifedipine</td>
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<td>Negative results</td>
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<td>Beta Blockers</td>
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<td>Carviodolol</td>
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<td></td>
<td></td>
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<td>Neg. results(animal)</td>
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</table>

Moshiri M. Etamad L.
<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
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<th>Animal study</th>
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<td>Lamotrigine</td>
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</table>
ILE in the treatment of acute poisoning:
a mini-review of human and animal studies.

Mechanisms

Mechanisms

- Four mechanisms are suggested
  1) Lipid sink
  2) Bioenergetics
  3) Ca channel activation
  4) positive inotrope

Mechanisms

1) Lipid sink:
One hypothesis is the lipid-sink theory, whereby adding a large amount of lipids to the blood "repartitions" the drug away from the site of toxicity and into the blood, he said. "This is a simple, pharmacokinetic explanation; it can be thought of as changing the volume of distribution."

In this mechanism: increasing metabolism, distribution, or partitioning of drugs away from receptors into lipid within tissues, not merely shifting equilibrium away from the end-organ to the plasma.

Mechanisms

1) Lipid sink:

Mechanisms

1) Lipid sink:

A. After lipid infusion showed levels of lipophilic drugs (bupropion) decreasing in parallel with serum triglyceride levels but the same dramatic relationship was not observed with nonlipophilic (lamotrigine)

B. Lipophilic drugs Response much better than non-lipophilic

Verapamil \((\log P: 3.8)\) versus nifedipine \((\log P: 2.2)\), propranolol \((\log P: 3.6)\) versus atenolol \((\log P: 0.23)\), clomipramine \((\log P: 5.2)\) versus amitriptyline \((\log P: 4.9)\)

**Basic Investigation**

Correlation of Plasma and Peritoneal Diasylate Clomipramine Concentration with Hemodynamic Recovery after Intralipid Infusion in Rabbits

Martyn Harvey, FACEM, MBChB, BHB, Grant Cave, FACEM, MBChB, BHB, and Kerry Hoggett, MBBS

**Table 2**

Peritoneal Diasylate Clomipramine Concentration and Extraction Ratio

<table>
<thead>
<tr>
<th></th>
<th>Saline ($n = 10$)</th>
<th>Lipid ($n = 10$)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma clomipramine</td>
<td>211.5 ± 72.1</td>
<td>196.5 ± 191.0</td>
<td>0.840</td>
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<tr>
<td>(μg/L) T39min</td>
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<tr>
<td>PD clomipramine</td>
<td>37.7 ± 13.8</td>
<td>366.2 ± 186.2</td>
<td>0.002</td>
</tr>
<tr>
<td>(μg/L)</td>
<td></td>
<td></td>
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<tr>
<td>ER clomipramine</td>
<td>0.20 ± 0.007</td>
<td>3.19 ± 2.38</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Data presented mean ± SD.  
ER = extraction ratio; PD = peritoneal diasylate.

**Mechanisms**

1) Lipid sink:

D. Weinberg have found that lipid treatment accelerates recovery from bupivacaine-induced asystole in the isolated rat heart, reduces bupivacaine myocardial tissue content, and increases cardiac bupivacaine washout.

Weinberg et al; (2006) Lipid Infusion Accelerates Removal of Bupivacaine and Recovery From Bupivacaine Toxicity in the Isolated Rat Heart; Reg Anesth Pain Med 31 296-303

**Mechanisms**

2) Bioenergetics

said Dr. Hoffman: "According to the [bioenergetics] theory, a large bolus of fatty acids provides energy substrate for the failing myocardium."

Local anaesthetics, and potentially other drugs, can *impair fatty acid transport* into *cardiac mitochondria* by inhibiting carnitine acylcarnitine translocase so *High plasma triglyceride concentrations might overwhelm such inhibition*

Mechanisms

3) Ca channel activation

The third potential mechanism is direct activation of the cardiac voltage-gated calcium channel, thereby increasing cytosolic calcium and increasing cardiac performance.

Mechanisms

4) positive inotrope

ILE acting as a positive inotrope

Stehr et al. have shown that lipid infusion is a positive inotrope in isolated heart and reverses bupivacaine-induced cardiac depression at lipid levels less than those needed to reduce aqueous bupivacaine concentration.


Conclusion
**Conclusion**

- Benefits from IFE in intoxication should be evaluated against standard therapy rather than with placebo and concomitantly with various antidotes to evaluate the potential for deleterious interactions.
- Further work is needed to confirm the usefulness of IFE in oral intoxication, the acceptable delay of administration after the ingestion, as well as the optimal type, dose, and duration of the IFE therapy.

Conclusion

✓ Dose adjustment for different patient population (pediatric, morbidly obese, hepatic, and renal-impaired patients) should be clarified. Long-term outcomes should be monitored and adverse effects should specifically be sought.
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