INTERNATIONAL CONFERENCE

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INTERNATIONAL CONFERENCE REGIONAL ANAESTHESIA

LA SYSTEMIC TOXICITY(LAST) AND INTRAVENOUS LIPID EMULSION (ILE)

(IN COLLABORATION WITH MALAYSIAN SIGRA)

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RAMSAY-SIME DARBY MEDICAL CENTRE ARA DAMANSARA, SELANGOR, MALAYSIA

MAYRA CABRERA

- 30yr/ OT nurse
- Delivered at 8:14am, 11 May 2004 in Britain
- 9am, felt dizzy, before fitted and suffered a cardiac arrest
- Resuscitated but unsuccessful, pronounced death at 10:47am
- Epidural catheter was wrongly connected to her iv line
- Died of Bupivacaine toxicity

Epidural drug death mother was unlawfully killed

rt attack. Photograph: PA

Hospital trust to pay £100,000 after new mother died when painkiller was attached to drip by mistake

By DAILY MAIL REPORTER
UPDATED: 14:43 GMT, 17 May 2010

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A hospital trust was ordered to pay £100,000 today after a mother who had just given birth died due to a mix-up between 'identical-looking' drugs.

Mayra Cabrera, 30, died hours after giving birth to son Zac, who survived, at Great Western Hospital in Swindon, Wiltshire, on May 11 2004.

A drip bag containing the powerful painkiller Bupivacaine was wrongly connected to a line into her right hand, administering a fatal dose of the drug.

Mrs Cabrera - who was a nurse at the same hospital - died within minutes from a heart attack caused by the toxic effects of Bupivacaine.

Mother's epidural death unlawful

A theatre nurse who died after wrongly having a drug used in epidurals pumped into her arm was unlawfully killed, an inquest jury has ruled.

Mayra Cabrera, 30, died shortly after giving birth to son Zac at the Great Western Hospital, Swindon, on 11 May 2004. The baby survived.

Epidural drip 'killed' mother
In quotes: reaction

INCIDENCE OF LAST

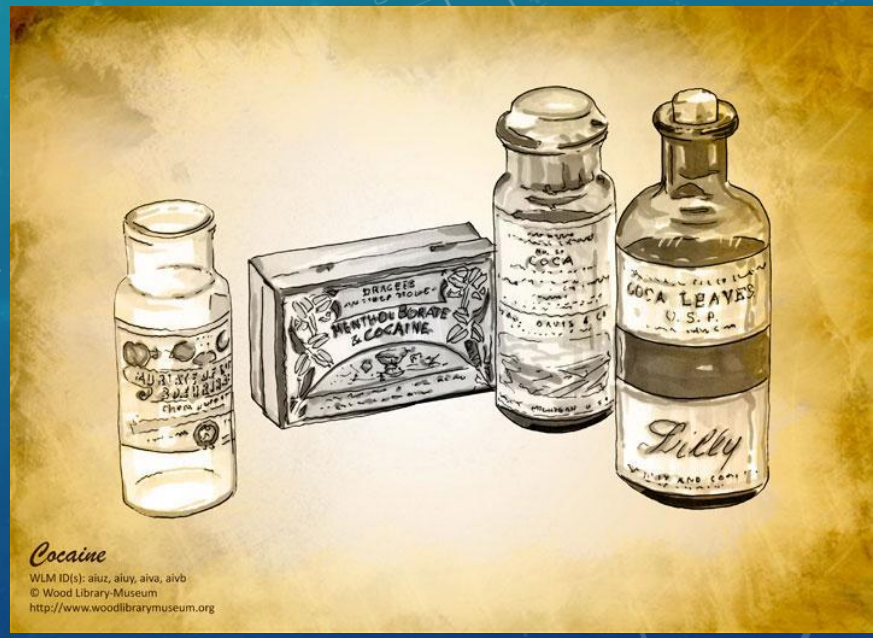
- Since the use of Cocaine in the late 19th century
- 1928, American Medical Association reported 40 deaths d/t LAST, majority cocaine & procaine
- Before 1981 epidural use for labor analgesia had reported LAST in 100 per 10,000 cases
- Mulroy MF (Reg Anesth Pain Med 2002), reported from 1993-1997, rate of LAST for epidural anaesthesia of 1.2-11 per 10,000 anaesthetics
- reported LAST for PNB was :

➢ 7.5 per 10,000 in 1997 (Auroy Y ,Anesthesiology 2002)

➢ 2.5 per 10,000 in 2004 (Auroy Y ,Anesthesiology 2002)

➢ 9.8 per 10,000 in 2009 (Barrington Mj, Rej Anesth Pain Med 2009)

➢ 8.7 per 10,000 in 2013 when using US (Barrington Mj, Reg Anesth Pain Med 2013)

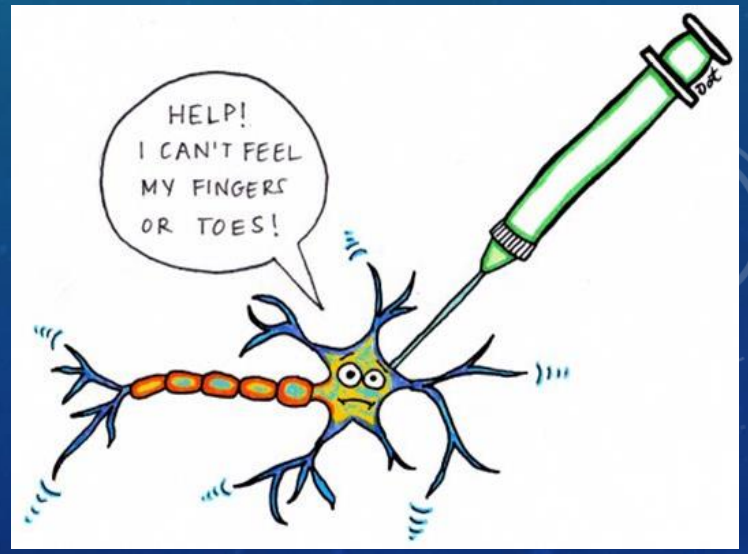


MECHANISM OF LA TOXICITY

- The actual mechanism remains elusive

Systemic absorption (delayed onset)

Accidental iv inj (rapid onset)



BRAIN

- LA affect the balance between inhibitory & excitatory pathway

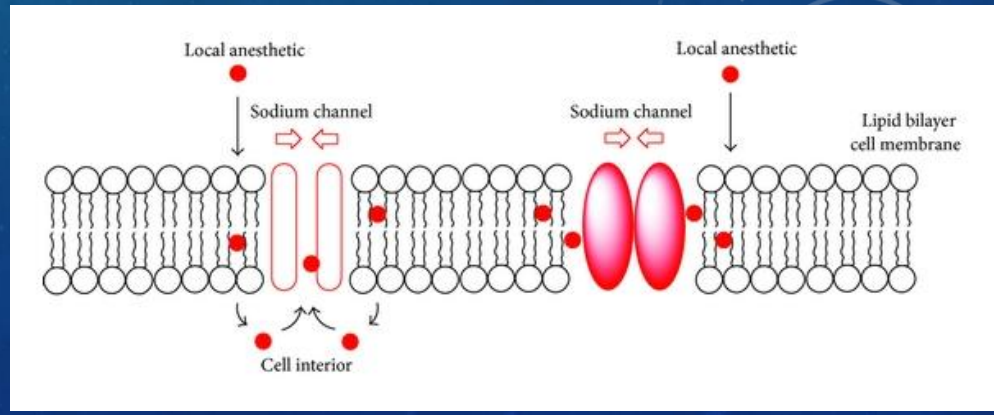
MECHANISM OF LA TOXICITY

HEART

- Conduction block - Na^+, K^+ & Ca^{++}

  → dysrhytmia & reduced contractility

- Disrupt intracellular signals originating at metabotropic receptors → ↓ cyclic adenosine monophosphate → reduce contractility



RISK FACTORS FOR LAST

1)LA - Type

- Dose

2) The block – site

- single vs continuous

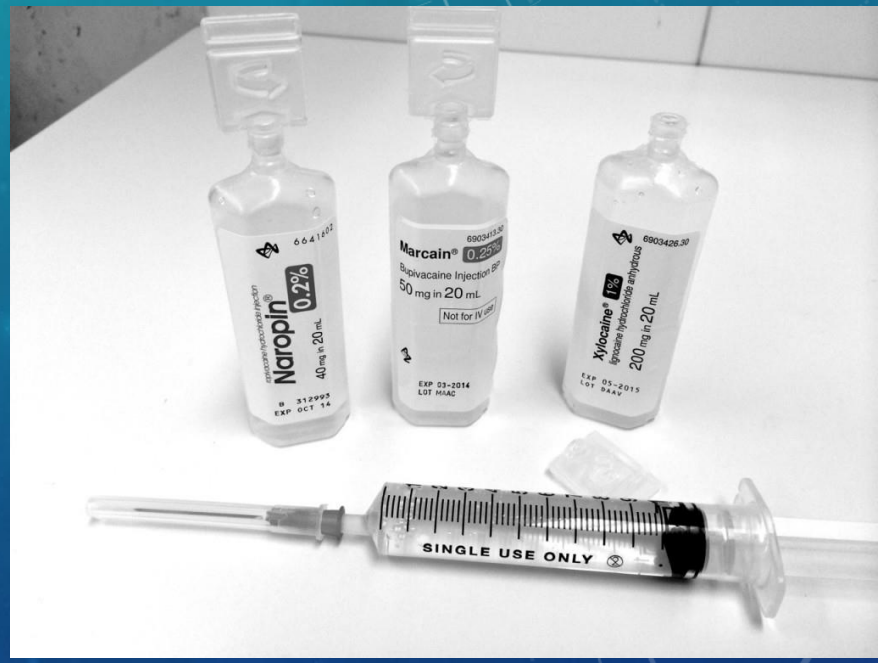
- conduct of block

3)The patient

RISK FACTORS FOR LAST

1) Type of LA

- Mazoit J (Anesth 1993)- more L-Bupivacaine than bupivacaine was required to induce cardiac arrest in rabbit hearts
- Huang Y (Anesth Analg 1998)- L-bupivacaine caused fewer convulsions and arrhythmias than bupivacaine
- L-bupivacaine & ropivacaine have intrinsic vasoconstriction properties that may prolong duration of action and slow systemic absorption → this may be safer than bupivacaine but the clinical significant of this difference remains unclear



RISK FACTORS FOR LAST

1) Type of LA

- Ropivacaine may cause less motor block, but whether it is clinically significantly less toxic is unknown
- LA with lower CC/CNS ratio can progress from CNS to CVS collapse faster ; bupivacaine(2.0) vs lidocaine (7.1)
- Indeed, it is not clear that any one agent is less toxic than another to a degree that is clinically relevant

RISK FACTORS FOR LAST

1) Dose of LA

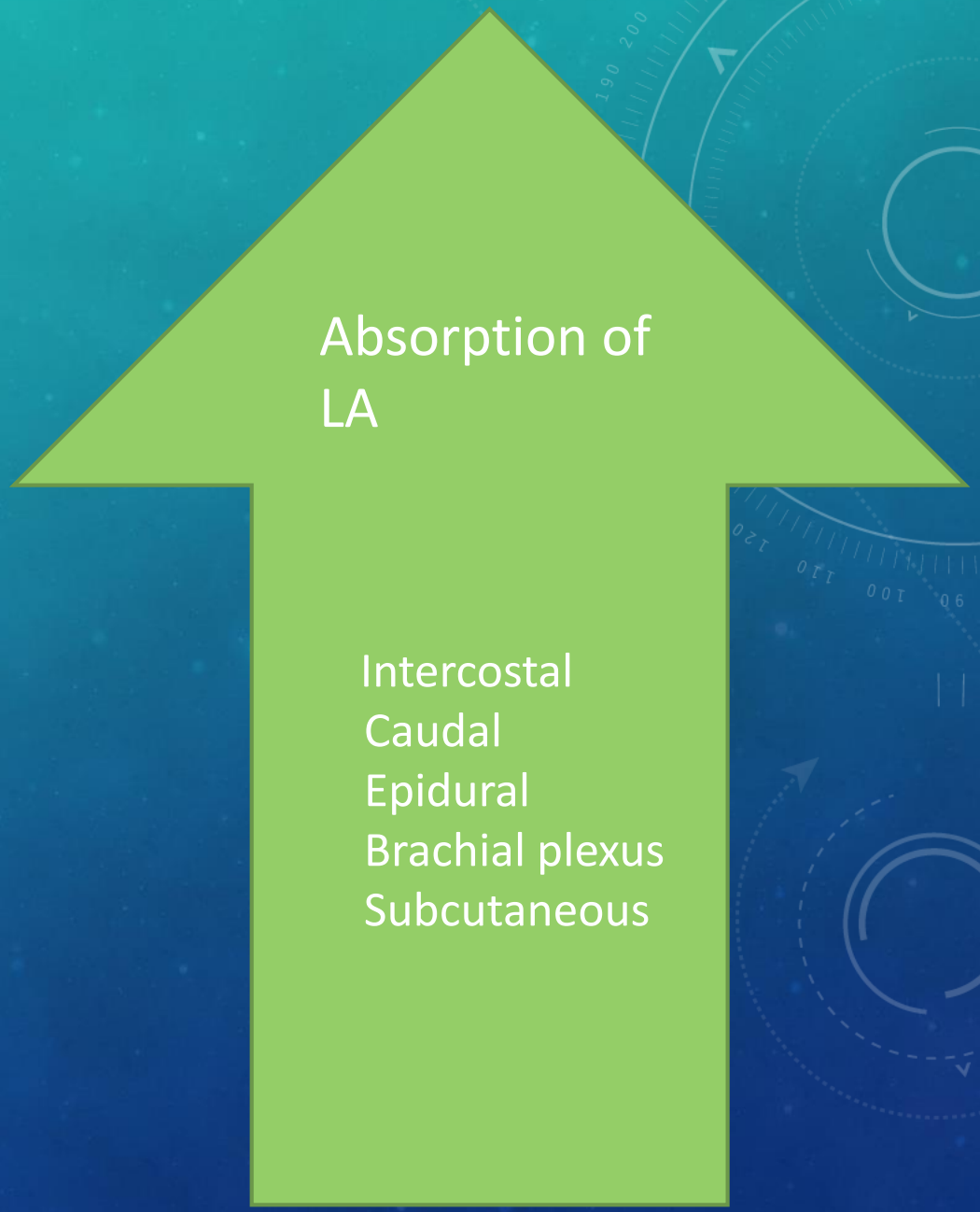
- The recommended maximum weight-based dose is not based on solid evidence, is just a rough guide for clinical use
  - ? Vary significantly between countries
  - ? Patient factors ?pregnant ?obese
  - ? Site of injection
  - ? Actual or ideal body weight
  - ? Co-morbidities of the patient
- Use the lowest effective dose

RISK FACTORS FOR LAST

2) Block related

a) Site of block

- higher risk of direct iv inj:
  - -interscalene
  - - stellate ganglion block
- higher risk of rapid absorption
  - - scalp
  - -bronchial mucosa
  - - pleura



RISK FACTORS FOR LAST

3) Block related

b) single vs continuous infusion

- continuous infusion → LA accumulation over time → delayed LAST

- continuous monitoring throughout the period of infusion

RISK FACTORS FOR LAST

2) Block related

c) Conduct of the block

- to reduce the risk of LAST

  - frequent aspiration

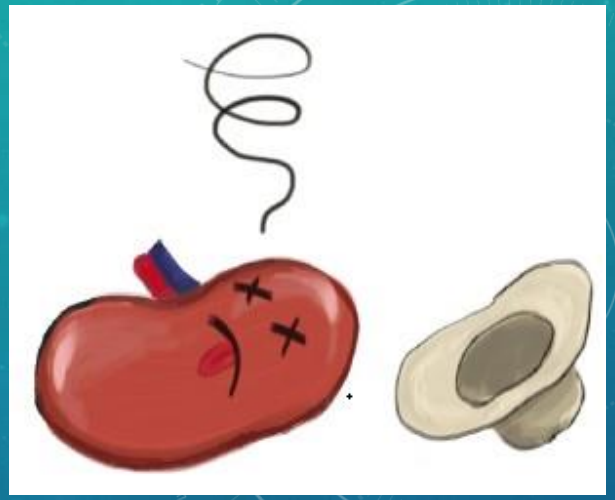
  - incremental injection

  - test dose

  -tracer , eg. Epinephrine (controversial)

  - US guided needle placement

RISK FACTORS FOR LAST



3) Patient related factors

a) Renal impairment

- a hyperdynamic circulation → ↑ systemic absorption
- a reduced clearance of LAs
- an ↑ α_1 - acid glycoprotein (AAG) → ↓ free LA conc.

=> overall ↑ toxicity risk

➡ recommended to ↓ dose by 10-20% according to the degree of renal impairment

RISK FACTORS FOR LAST

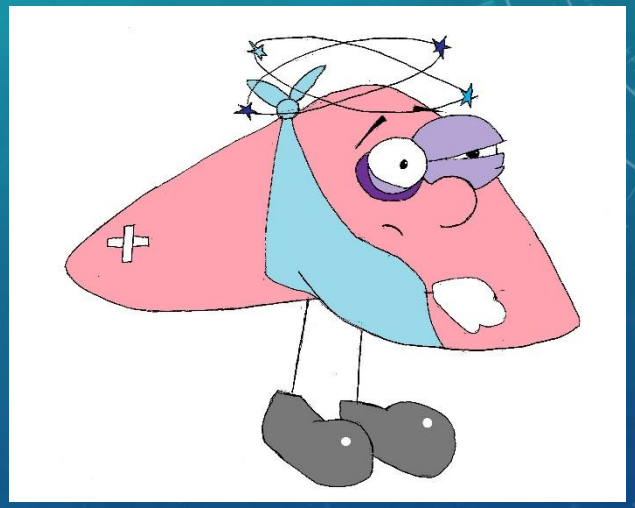
3) Patient related factors

b) Liver disease

- ↓ LA clearance

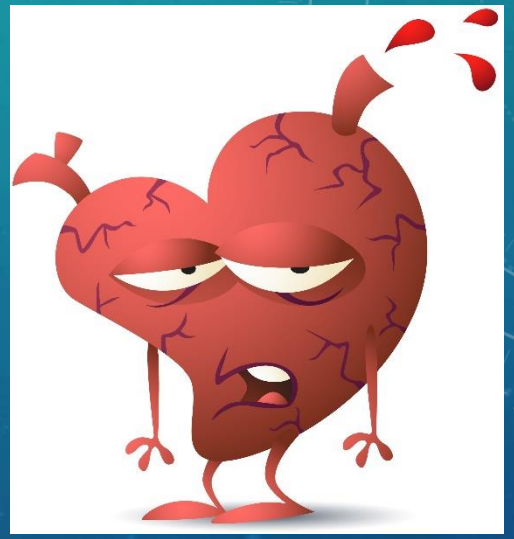
- single dose unaffected

- but doses for repeated boluses & continuous infusion should be reduced



RISK FACTORS FOR LAST

3) Patient related factors



c) Severe heart failure

- susceptible to LA induced myocardial depression & arrhythmia

- lower liver and renal perfusion slows the metabolism & elimination of LA

→ recommended to reduce initial & maintenance doses of LA

RISK FACTORS FOR LAST

3) Patient related factors

d) Elderly patients

- ↓ blood flow and ↓organ function ,lowers clearance

- multiple co-morbidities altering LA pharmacokinetics & pharmacodynamics

- nerves appear more sensitive to LA block d/t reduction in axonal function, altered nerve morphology & reduced surrounding fatty tissue

➡ recommended to reduce the LA doses

RISK FACTORS FOR LAST

3) Patient related factors

e) Pediatrics patients

- they have reduced α_1 - acid glycoprotein (AAG)
- ↑elimination t½ of LAs
- this ↑ the risk of accumulation with continuous infusion

RISK FACTORS FOR LAST

3) Patient related factors

f) Pregnant patients

- lower AAG levels

- accelerated perfusion of sites of injection

→ increase absorption of LAs

SIGN & SYMPTOM OF LAST

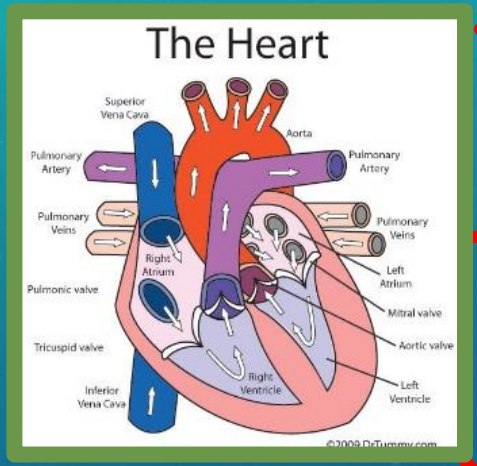
Excitatory state

- Perioral tingling
- Tinnitus
- Slurred speech
- Light headedness
- Tremor
- Confusion/ agitation
- convulsion

Depressive phase

- Coma
- Respiratory depression

SIGN & SYMPTOM OF LAST



Initial phase

- Hypertension
- Tachycardia

Intermediate phase

- Myocardial depression
- Hypotension

Terminal phase

- Peripheral vasodilatation
- Severe hypotension
- Arrhythmia- sinus bradycardia, conduction block, VT, VF & asystole

ILE IN LAST!

-BRIEF HISTORY

Anesthesiology. 1998 Apr;88(4):1071-5.

Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats.

Weinberg GL[1], VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ.

⊕ Author information

Abstract

BACKGROUND: The authors sought to confirm a chance observation that intravenous lipid treatment increases the dose of bupivacaine required to produce asystole in rats. The authors also measured the partitioning of bupivacaine between the lipid and aqueous phases of a plasma-lipid emulsion mixture.

METHODS: Anesthetized Sprague-Dawley rats were used in pretreatment (protocol 1) and resuscitation (protocol 2) experiments. In protocol 1, animals were pretreated with saline or 10%, 20%, or 30% Intralipid (n = 6 for all groups), then received 0.75% bupivacaine hydrochloride at a rate of 10 ml x kg x min(-1) to asystole. In protocol 2, mortality was compared over a range of bolus doses of bupivacaine after resuscitation with either saline or 30% Intralipid (n = 6 for all groups). The lipid:aqueous partitioning of bupivacaine in a mixture of plasma and Intralipid was measured using radiolabeled bupivacaine.

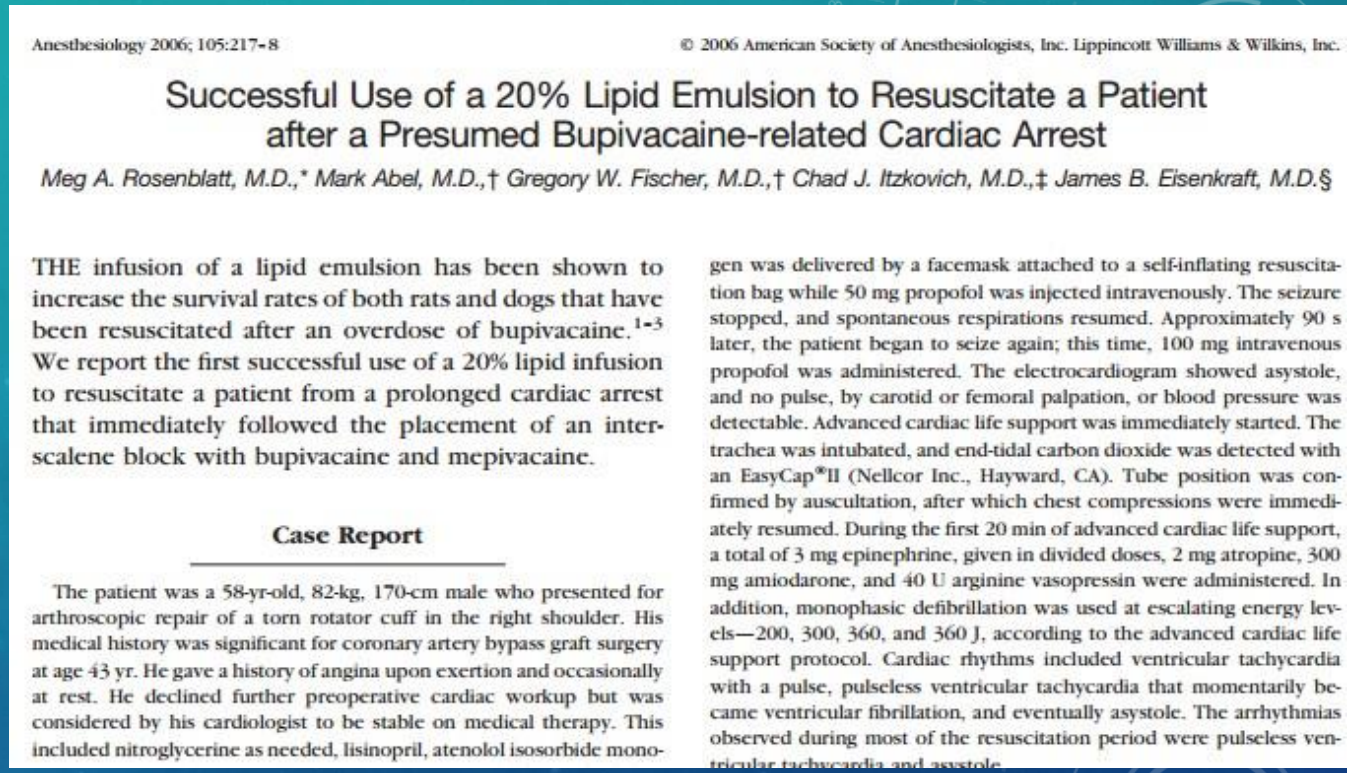
RESULTS: Median doses of bupivacaine (in milligrams per kilogram) producing asystole in protocol 1 were for 17.7 for saline, 27.6 for 10% Intralipid, 49.7 for 20% Intralipid, and 82.0 for 30% Intralipid ($P < 0.001$ for differences between all groups). Differences in mean +/- SE concentrations of bupivacaine in plasma (in micrograms per milliliter) were significant ($P < 0.05$) for the difference between saline (93.3 +/- 7.6) and 30% Intralipid (212 +/- 45). In protocol 2, lipid infusion increased the dose of bupivacaine required to cause death in 50% of animals by 48%, from 12.5 to 18.5 mg/kg. The mean lipid:aqueous ratio of concentrations of bupivacaine in a plasma-Intralipid mixture was 11.9 +/- 1.77 (n = 3).

CONCLUSIONS: Lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Partitioning of bupivacaine into the newly created lipid phase may partially explain this effect. These results suggest a potential application for lipid infusion in treating cardiotoxicity resulting from bupivacaine.

- 1998, Weinberg G
- First report of successful use of ILE in LAST in a rats model

FIRST SUCCESSFUL CASE OF ILE IN LAST IN HUMAN

- 2006, Rosenblatt et al
- 58/man, shoulder surgery
- Developed cardiac arrest 30 sec after NSG interscalene block with mixture of bupivacaine & mepivacaine
- Failed to respond to ACLS
- 20min later 100ml of 20% intralipid was given
- Achieved normal v/s within second
- No neurologic sequelae



Anesthesiology 2006; 105:217–8

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.§*

THE infusion of a lipid emulsion has been shown to increase the survival rates of both rats and dogs that have been resuscitated after an overdose of bupivacaine.[1–3] We report the first successful use of a 20% lipid infusion to resuscitate a patient from a prolonged cardiac arrest that immediately followed the placement of an interscalene block with bupivacaine and mepivacaine.

Case Report

The patient was a 58-yr-old, 82-kg, 170-cm male who presented for arthroscopic repair of a torn rotator cuff in the right shoulder. His medical history was significant for coronary artery bypass graft surgery at age 43 yr. He gave a history of angina upon exertion and occasionally at rest. He declined further preoperative cardiac workup but was considered by his cardiologist to be stable on medical therapy. This included nitroglycerine as needed, lisinopril, atenolol isosorbide monogen was delivered by a facemask attached to a self-inflating resuscitation bag while 50 mg propofol was injected intravenously. The seizure stopped, and spontaneous respirations resumed. Approximately 90 s later, the patient began to seize again; this time, 100 mg intravenous propofol was administered. The electrocardiogram showed asystole, and no pulse, by carotid or femoral palpation, or blood pressure was detectable. Advanced cardiac life support was immediately started. The trachea was intubated, and end-tidal carbon dioxide was detected with an EasyCap®II (Nellcor Inc., Hayward, CA). Tube position was confirmed by auscultation, after which chest compressions were immediately resumed. During the first 20 min of advanced cardiac life support, a total of 3 mg epinephrine, given in divided doses, 2 mg atropine, 300 mg amiodarone, and 40 U arginine vasopressin were administered. In addition, monophasic defibrillation was used at escalating energy levels—200, 300, 360, and 360 J, according to the advanced cardiac life support protocol. Cardiac rhythms included ventricular tachycardia with a pulse, pulseless ventricular tachycardia that momentarily became ventricular fibrillation, and eventually asystole. The arrhythmias observed during most of the resuscitation period were pulseless ventricular tachycardia and asystole

THE FIRST SUCCESSFUL CASE OF ILE IN TREATING NON-LA DRUG TOXICITY

Ann Emerg Med. 2008 Apr;51(4):412-5, 415.e1. Epub 2007 Sep 4.

Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine.

Sirianni AJ[1], Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, Weinberg GL, Henretig FM.

Author information

Abstract

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 intentional ingestion of up to 7.95 g of bupropion and 4 g of lamotrigine. Standard cardiopulmonary resuscitation for 70 minutes was unsuccessful in restoring sustained circulation. A 100-mL intravenous bolus of 20% lipid emulsion was then administered, and after 1 minute an effective sustained pulse was observed. The patient subsequently manifested significant acute lung injury but had rapid improvement in cardiovascular status and recovered, with near-normal neurologic function. Serum bupropion levels before and after lipid infusion paralleled triglyceride levels. This patient developed cardiovascular collapse because of intentional, oral overdose of bupropion and lamotrigine that was initially refractory to standard resuscitation measures. An infusion of lipid emulsion was followed rapidly by restoration of effective circulation. Toxicologic studies are consistent with the lipid sink theory of antidotal efficacy.

- 2008, Sirianni et al
- An adolescent suffered cardiac arrest d/t massive overdose of buprobion and lamotrigine
- Not responding to ACLS
- 90 min later, a bolus of ILE was given
- Recovered normal v/s within 1 min
- No major neurologic deficit

ILE IN NON-LA LIPOPHILIC DRUG

A) Tricyclic antidepressant

-dosulepin

-imipramine

-amitriptyline

B) Other antidepressant/antipsychotic

-lamotrigine

-hydroxyzine

-haloperidol

-bupropion

-olanzapine

-venlafaxine

-sertraline

-quetiapine

C) Organophosphate poisoning

D) Antiarrhythmic

-verapamil

-atenolol

-flecainide

E) B blockers

-propranolol

-nevibolol

F) Ca^{++} channel blocker

-diltiazem

-amlodipine

G) Glophosate herbicite

H) Anthelmintic

-moxidectin

I) Multi drug overdose

WHAT IS LIPID EMULSION ?

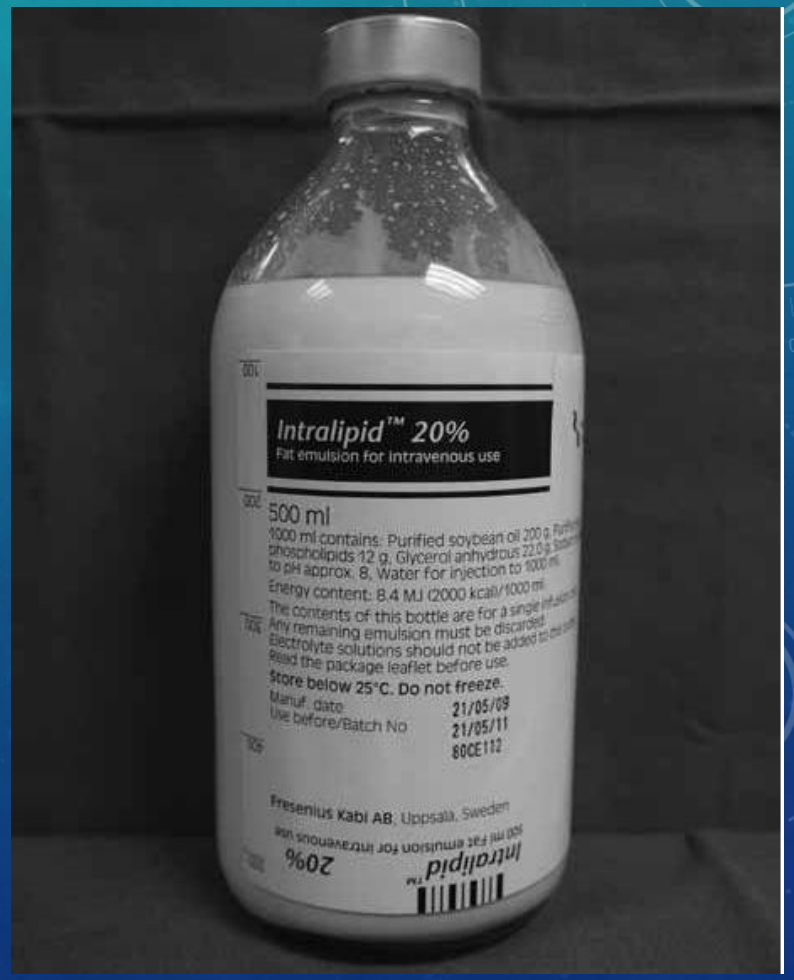
LIPID EMULSION

- A fat emulsion ,approved in 1962 in Europe
- Used as a component of TPN
- 1st brand name being “Intralipid”
- It is an emulsion of
  - soy bean oil
  - egg phospholipids
  - glycerin
- Available in 10%, 20% & 30% concentration

20%INTRALIPID

- 20% soy bean oil, predominantly unsaturated long chain fatty acid (FA)
- 1.2% egg yolk phospholipids
- 2.25% glycerin
- Water
- Sodium hydroxide to adjust the pH to 8.0

- Major component of FA:
  - linoleic acid 44-62%
  - oleic acid 19-30%
  - palmitic acid 7-14%
  - linolenic acid 4-11%
  - stearic acid 1.4-5.5%



MECHANISM OF ACTION OF ILE IN LAST

1) Lipid sink theory

- acts as a ‘sink’ to capture the lipophilic LAs

- the ILE binds the offending toxin to pull drug from the target tissue, thereby reversing the toxicity

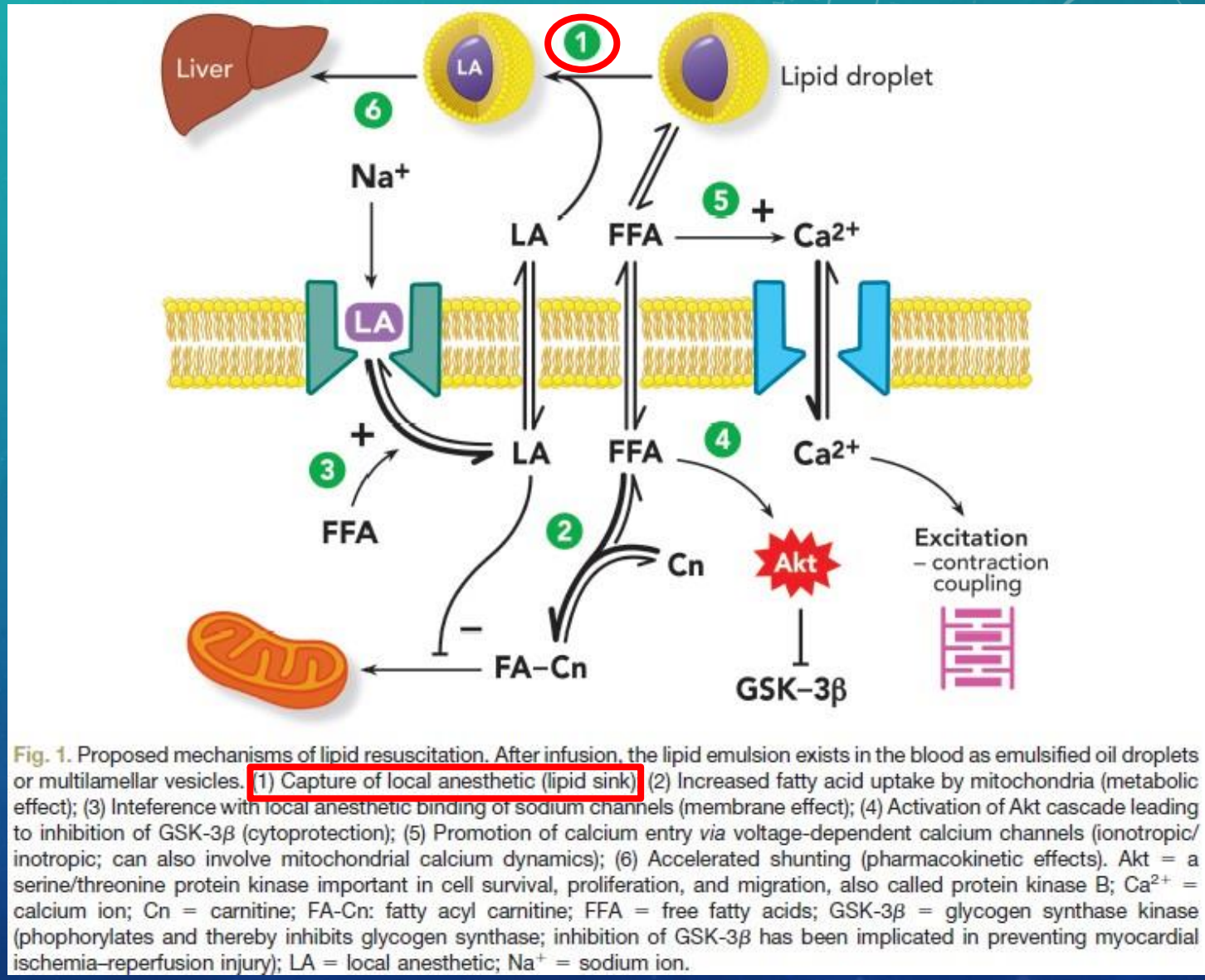


Fig. 1. Proposed mechanisms of lipid resuscitation. After infusion, the lipid emulsion exists in the blood as emulsified oil droplets or multilamellar vesicles. (1) Capture of local anesthetic (lipid sink) (2) Increased fatty acid uptake by mitochondria (metabolic effect); (3) Inteference with local anesthetic binding of sodium channels (membrane effect); (4) Activation of Akt cascade leading to inhibition of GSK-3β (cytoprotection); (5) Promotion of calcium entry *via* voltage-dependent calcium channels (ionotropic/inotropic; can also involve mitochondrial calcium dynamics); (6) Accelerated shunting (pharmacokinetic effects). Akt = a serine/threonine protein kinase important in cell survival, proliferation, and migration, also called protein kinase B; Ca^{2+} = calcium ion; Cn = carnitine; FA-Cn: fatty acyl carnitine; FFA = free fatty acids; GSK-3β = glycogen synthase kinase (phophorylates and thereby inhibits glycogen synthase; inhibition of GSK-3β has been implicated in preventing myocardial ischemia–reperfusion injury); LA = local anesthetic; Na^{+} = sodium ion.

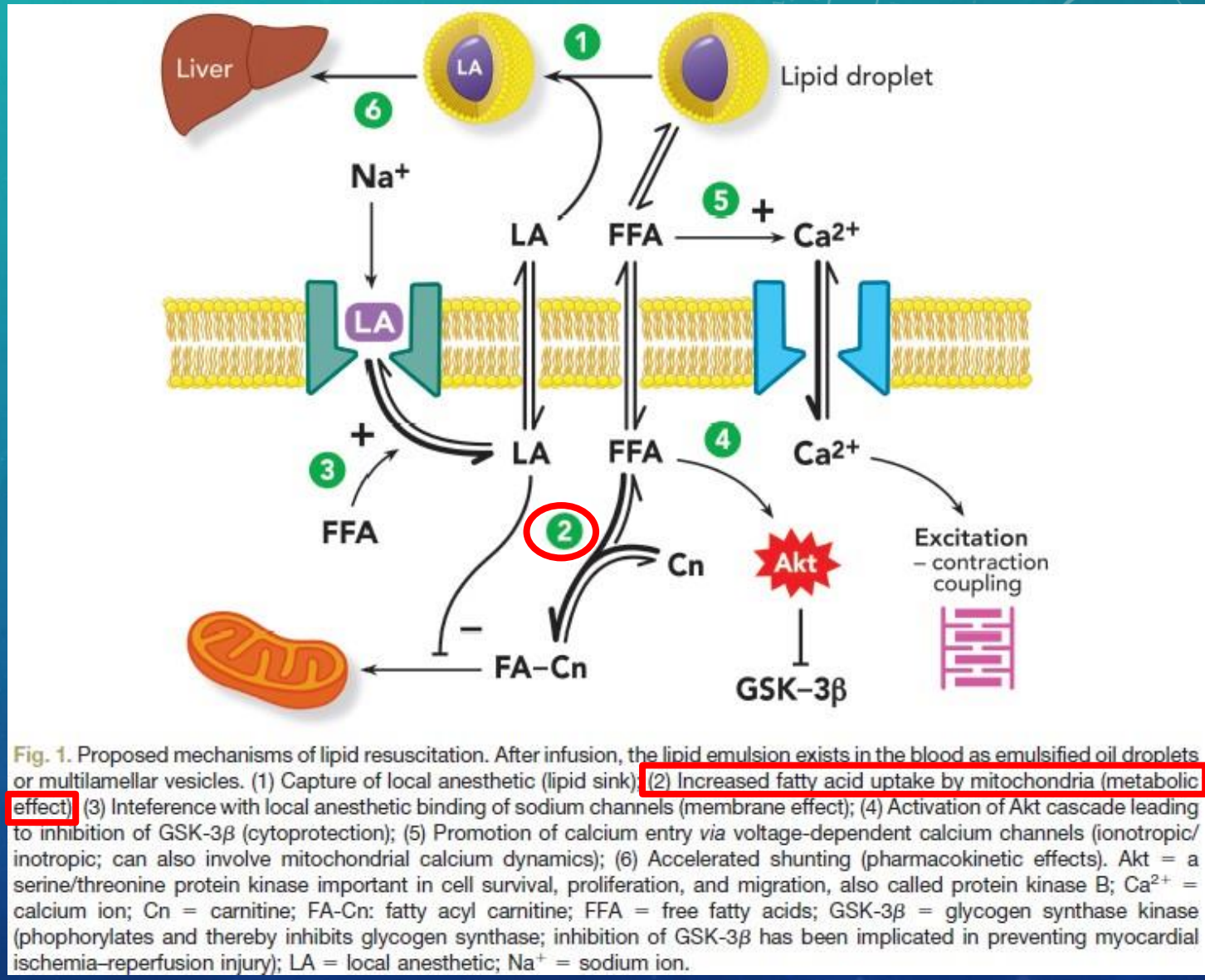
MECHANISM OF ACTION OF ILE IN LAST

2) Metabolic effect

- increase FA uptake by mitochondria

-augment the mitochondria FA metabolism

(lipids comprise the heart's preferred energy substrate under normal aerobic conditions)



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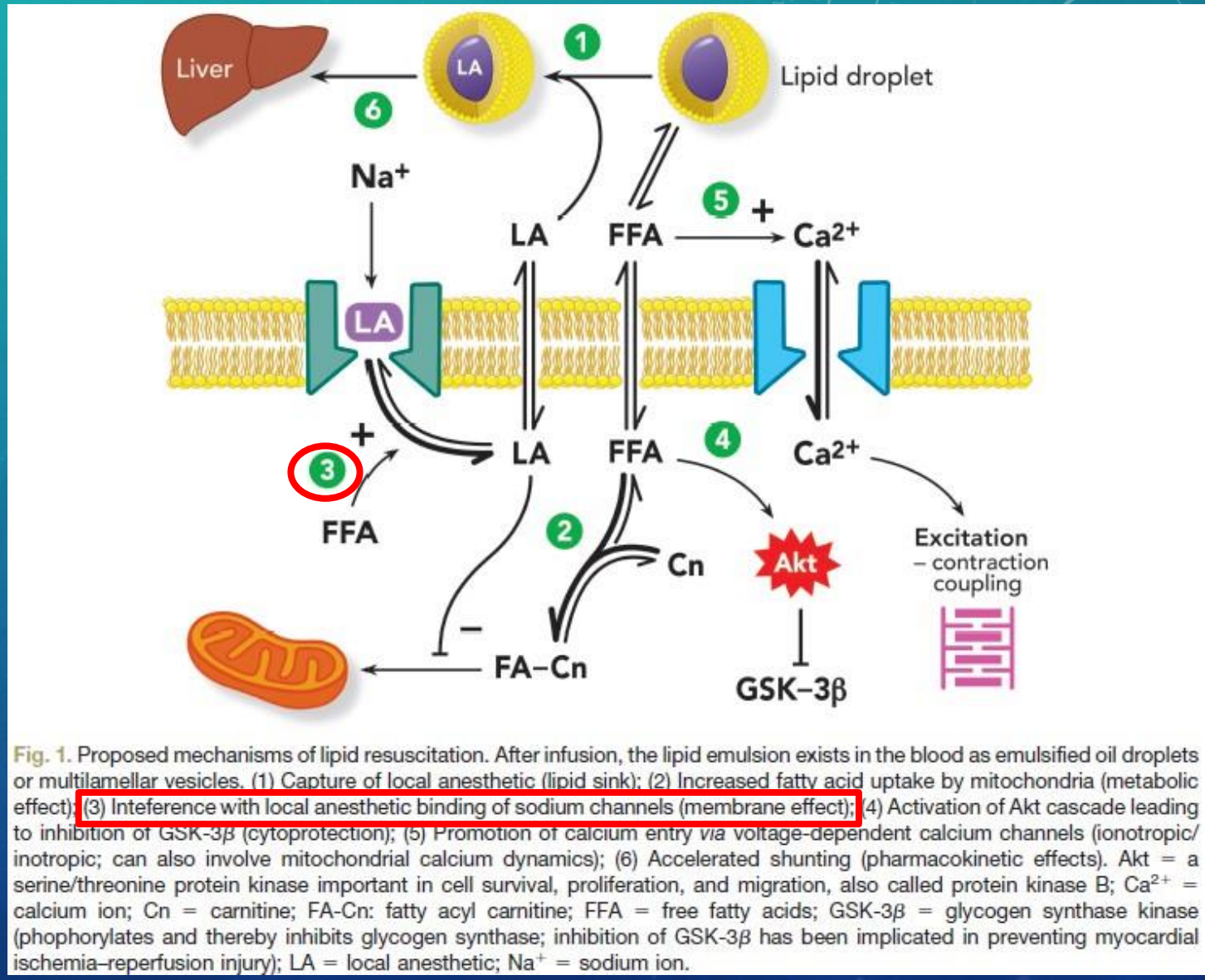
MECHANISM OF ACTION OF ILE IN LAST

3) Through competition/ membrane effect

- may directly inhibit LAs binding to cardiac Na^+ channels



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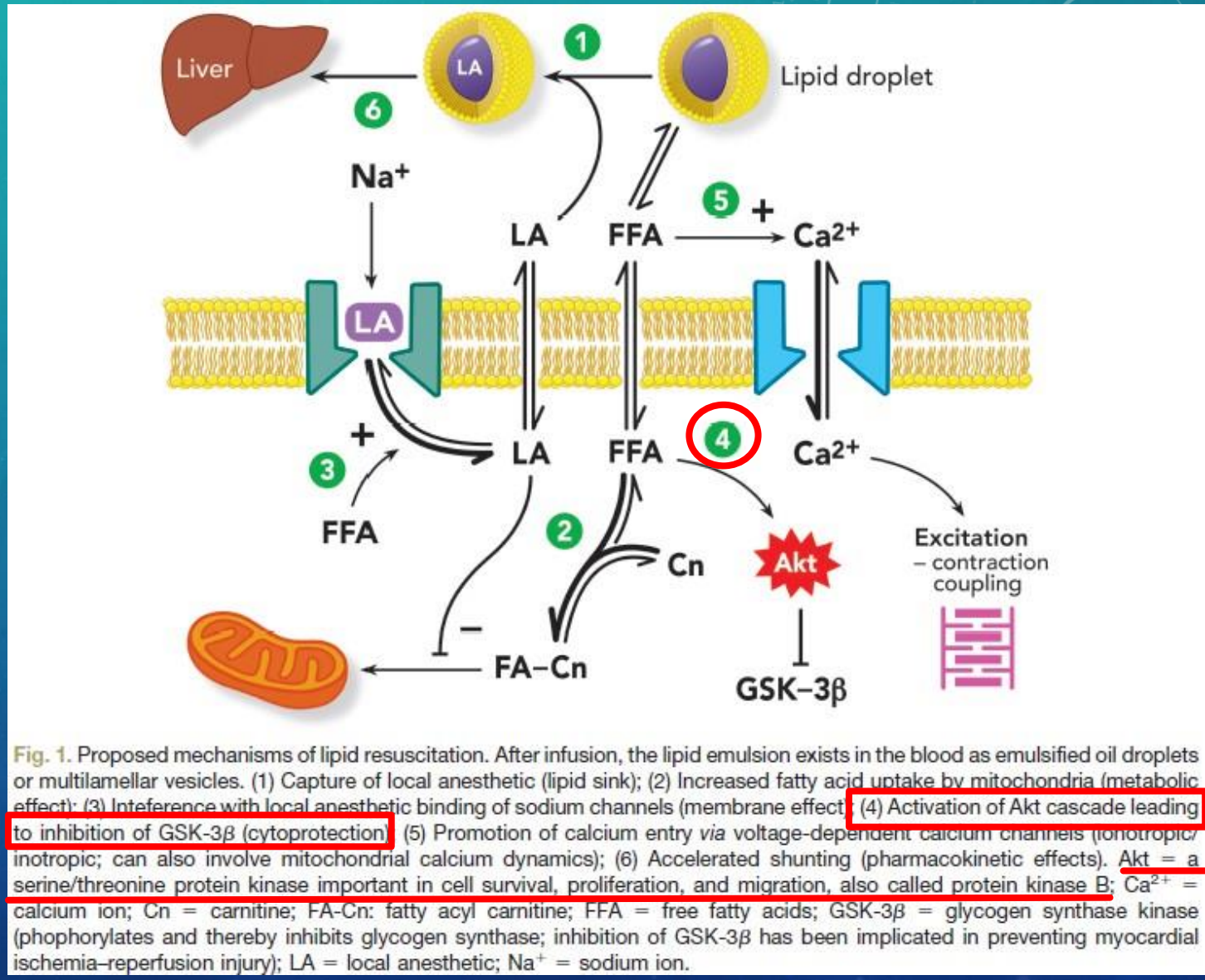
MECHANISM OF ACTION OF ILE IN LAST

4) Cytoprotective effect

- by activation of Akt (proteinkinase B), an enzyme important in cell survival & proliferation



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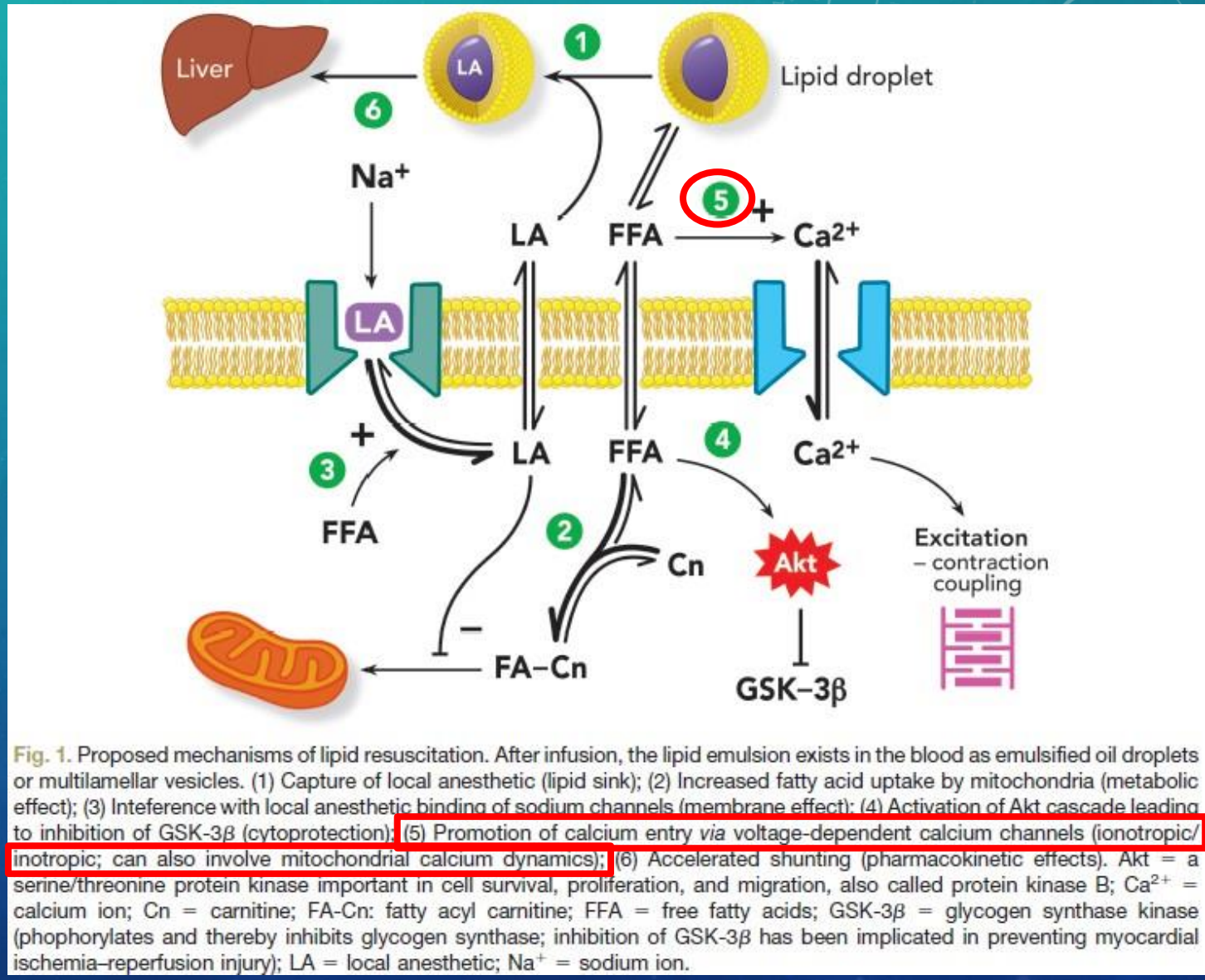
MECHANISM OF ACTION OF ILE IN LAST

5) Direct inotrope

- by increasing intracellular Ca^{2+} concentration



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MECHANISM OF ACTION OF ILE IN LAST

6) Pharmacokinetic effects

- accelerated shunting to sequestering organs

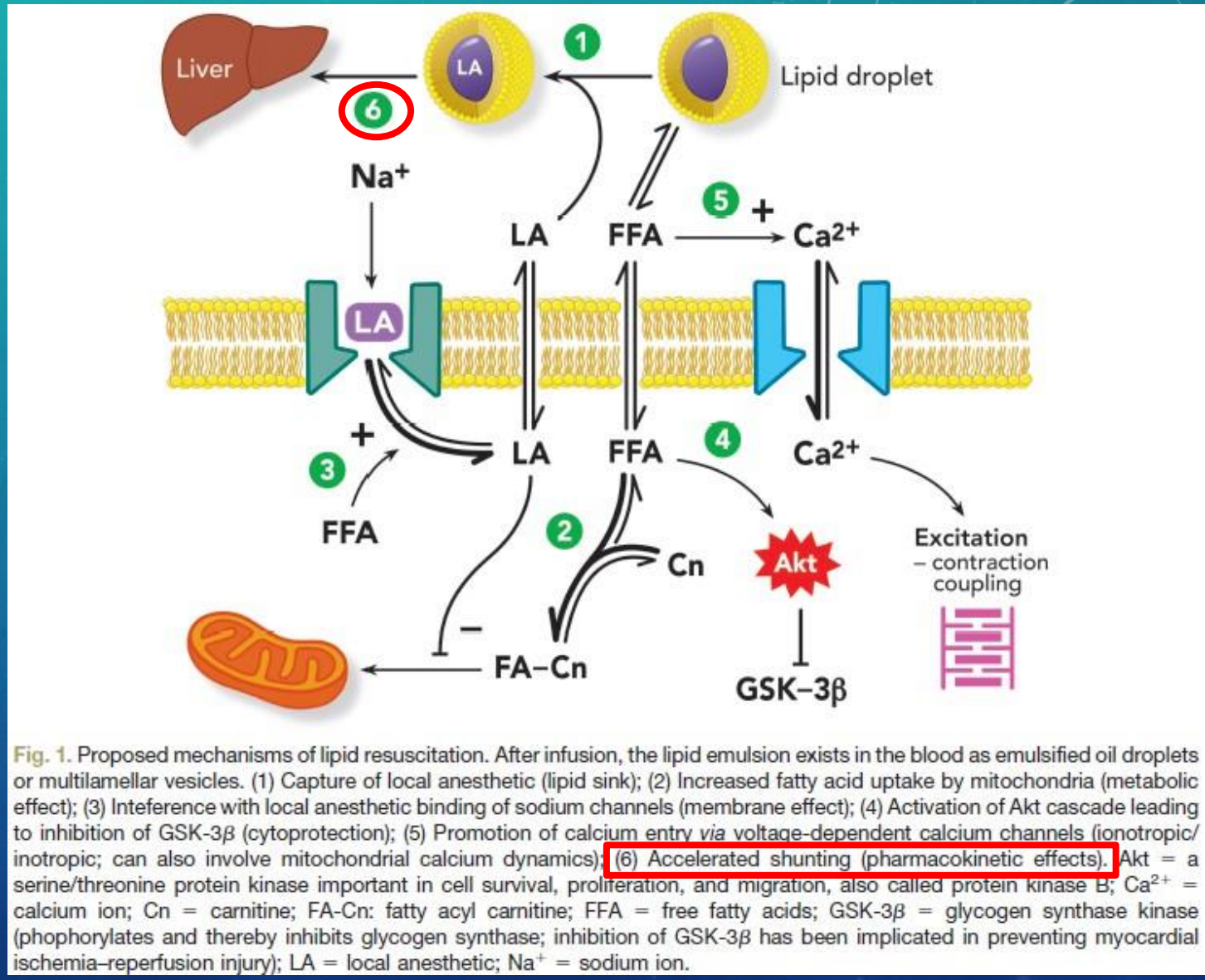
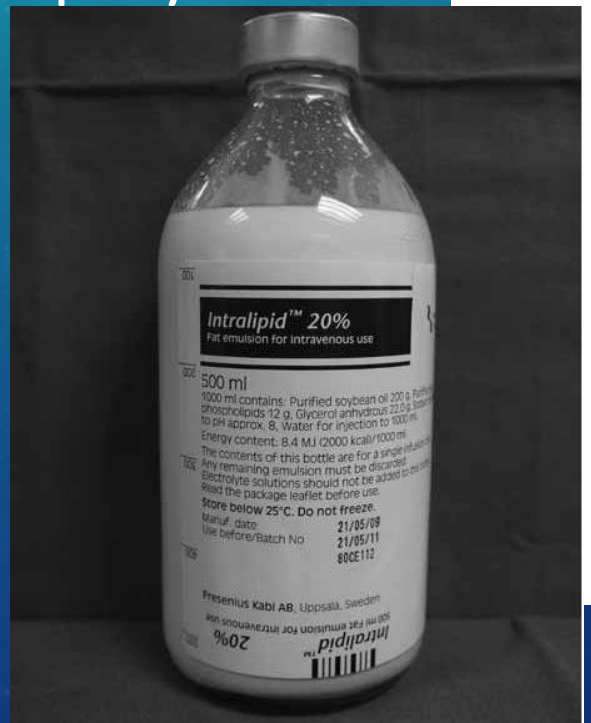


Fig. 1. Proposed mechanisms of lipid resuscitation. After infusion, the lipid emulsion exists in the blood as emulsified oil droplets or multilamellar vesicles. (1) Capture of local anesthetic (lipid sink); (2) Increased fatty acid uptake by mitochondria (metabolic effect); (3) Inteference with local anesthetic binding of sodium channels (membrane effect); (4) Activation of Akt cascade leading to inhibition of GSK-3β (cytoprotection); (5) Promotion of calcium entry *via* voltage-dependent calcium channels (ionotropic/inotropic; can also involve mitochondrial calcium dynamics); (6) Accelerated shunting (pharmacokinetic effects). Akt = a serine/threonine protein kinase important in cell survival, proliferation, and migration, also called protein kinase B; Ca^{2+} = calcium ion; Cn = carnitine; FA-Cn: fatty acyl carnitine; FFA = free fatty acids; GSK-3β = glycogen synthase kinase (phophorylates and thereby inhibits glycogen synthase; inhibition of GSK-3β has been implicated in preventing myocardial ischemia–reperfusion injury); LA = local anesthetic; Na^+ = sodium ion.

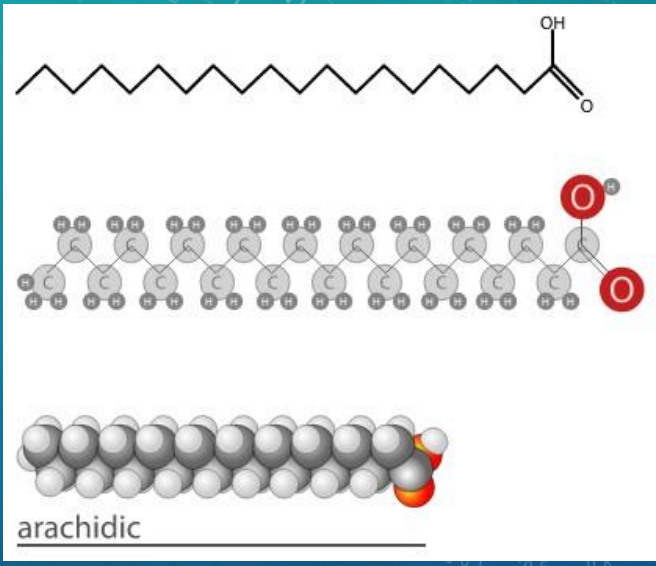
WHICH LIPID EMULSION (LE)?

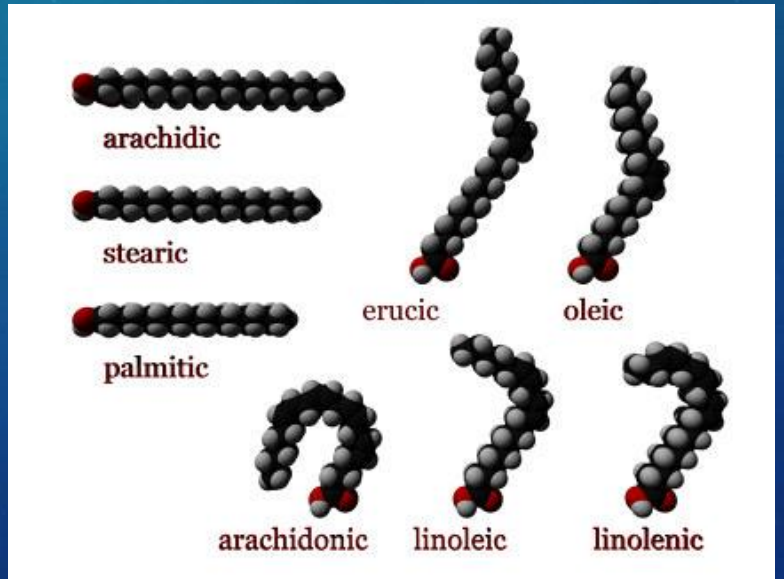
- 10% ? 20%? 30%?
- Long chain FA (LCFA)? Medium chain FA (MCFA)?
- Intralipid? Medialipide? Liposyn III ? Lipofundin?



WHICH LIPID EMULSION (LE)?

- Intralipid 20% was used in majority of the studies published on lipid rescue in LAST
- From a physio-chemical perspective, LE with LCFA seen to have an advantage, but laboratory study showed mixed result





WHICH LIPID EMULSION (LE)?

Anesthesiology. 2009 Feb;110(2):380-6. doi: 10.1097/ALN.0b013e318194b252.

Binding of long-lasting local anesthetics to lipid emulsions.

Mazoit JX[1], Le Guen R, Beloeil H, Benhamou D.

⊕ Author information

Abstract

BACKGROUND: Rapid infusion of lipid emulsion has been proposed to treat local anesthetic toxicity. The authors wanted to test the buffering properties of two commercially available emulsions made of long- and of long- and medium-chain triglycerides.

METHODS: Using the shake-flask method, the authors measured the solubility and binding of racemic bupivacaine, levobupivacaine, and ropivacaine to diluted Intralipid (Fresenius Kabi, Paris, France) and Medialipide (B-Braun, Boulogne, France).

RESULTS: The apparent distribution coefficient expressed as the ratio of mole fraction was 823 +/- 198 and 320 +/- 65 for racemic bupivacaine and levobupivacaine, and ropivacaine, respectively, at 500 mg in the Medialipide/buffer emulsion; and 1,870 +/- 92 and 1,240 +/- 14 for racemic bupivacaine and levobupivacaine, and ropivacaine, respectively, in the Intralipid/buffer emulsion. Decreasing the pH from 7.40 to 7.00 of the Medialipide/buffer emulsion led to a decrease in ratio of molar concentration from 121 +/- 3.8 to 46 +/- 2.8 for bupivacaine, and to a lesser extent from 51 +/- 4.0 to 31 +/- 1.6 for ropivacaine. The capacity of the 1% emulsions was 871 and 2,200 microM for the 1% Medialipide and Intralipid emulsions, respectively. The dissociation constant was 818 and 2,120 microM for racemic bupivacaine and levobupivacaine, and ropivacaine, respectively. Increasing the temperature from 20 to 37 degrees C led to a greater increase in affinity for ropivacaine (55%) than for bupivacaine (27%). When the pH of the buffer was decreased from 7.40 to 7.00, the affinity was decreased by a factor of 1.68, similar for both anesthetics.

CONCLUSIONS: The solubility of long-acting local anesthetics in lipid emulsions and the high capacity of binding of these emulsions most probably explain their clinical efficacy in case of toxicity. The long-chain triglyceride emulsion Intralipid appears to be about 2.5 times more efficacious than the 50/50 medium-chain/long-chain Medialipide emulsion. Also, because of their higher hydrophobicity, racemic bupivacaine and levobupivacaine seem to clear more rapidly than ropivacaine.

- 2009, Mazoit et al
- Compared Intralipid (LCFA) & Medialipide (LCFA/MCFA) in their binding capacity for racemic bupivacaine, L-bupivacaine & ropivacaine
- Intralipid was 2.5X more efficacious
- But it is unclear in actual clinical efficacy
- Also found that low pH reduced lipid binding of LAs

WHICH LIPID EMULSION (LE)?

Anesthesiology. 2012 Feb;116(2):334-9. doi: 10.1097/ALN.0b013e318242a5f1.

A mixed (long- and medium-chain) triglyceride lipid emulsion extracts local anesthetic from human serum in vitro more effectively than a long-chain emulsion.

Ruan W[1], French D, Wong A, Drasner K, Wu AH.

⊕ Author information

Abstract

BACKGROUND: Lipid emulsion infusion reverses cardiac toxicity of local anesthetics. The predominant effect is likely creation of a "lipid sink." This in vitro study determined the extent to which Intralipid® (Fresenius Kabi, Uppsala, Sweden) and Lipofundin® (B. Braun Melsungen AG, Melsungen, Germany) sequester anesthetics from serum, and whether it varies with pH.

METHODS: Bupivacaine, ropivacaine, and mepivacaine were added to human drug-free serum (pH 7.4) at 10 μg/ml. The lipid emulsions were added, and the mixture shaken and incubated at 37°C. Lipid was removed by ultracentrifugation and drug remaining in the serum measured. Additional experiments were performed using 100 μg/ml bupivacaine and at pH 6.9.

RESULTS: Lipofundin® extracted all three anesthetics to a greater extent than Intralipid® (34.7% vs..22.3% for bupivacaine, 25.8% vs..16.5% for ropivacaine, and 7.3% vs..4.7% for mepivacaine). By increasing either concentration of bupivacaine or lipid, there was an increase in drug extraction from serum. Adjusting the pH to 6.9 had no statistically significant effect on the percentage of bupivacaine sequestered.

CONCLUSIONS: Bupivacaine, ropivacaine, and mepivacaine were sequestered to an extent consistent with their octanol:water partition constants (logP). In contrast with previous studies of extraction of lipids from buffer solutions, an emulsion containing 50% each of medium- and long-chain triglycerides extracted local anesthetics to a greater extent from human serum than one containing exclusively long-chain triglycerides, calling into question recent advanced cardiac life support guidelines for resuscitation from anesthetic toxicity that specify use of a long-chain triglyceride. The current data also do not support recent recommendations to delay administration until pH is normalized.

- 2012, Ruan et al
- Reported that an LCT/MCT (50:50) mixture extracted bupivacaine, ropivacaine & mepivacaine better than LCT emulsion

WHICH LIPID EMULSION (LE)?

Anesthesiology. 2011 Dec;115(6):1219-28. doi: 10.1097/ALN.0b013e318238be73.

Lipid resuscitation of bupivacaine toxicity: long-chain triglyceride emulsion provides benefits over long- and medium-chain triglyceride emulsion.

Li Z[1], Xia Y, Dong X, Chen H, Xia F, Wang X, Dong H, Jin Z, Ding X, Papadimos TJ, Xu X.

⊕ Author information

Abstract

BACKGROUND: The superiority of Intralipid, a long-chain triglyceride (LCT) emulsion versus Lipovenoes, a long- and medium-chain triglyceride (LCT/MCT) emulsion, in reversing local anesthetic-induced cardiac arrest is poorly defined and needs to be determined.

METHODS: The study included two parts: in experiment A, bupivacaine (20 mg/kg) was injected to produce asystole. Either Intralipid 20% (LCT group, n = 30) or Lipovenoes 20% (LCT/MCT group, n = 30) with epinephrine was infused immediately. Return of spontaneous circulation and recurrence of asystole after resuscitation were recorded. In experiment B, 80 rats using the same model and resuscitation protocol were divided into 10 groups: LCT_0, LCT_{15}, LCT_{30}, LCT_{60}, and LCT_{120} and LCT/MCT_0, LCT/MCT_{15}, LCT/MCT_{30}, LCT/MCT_{60}, and LCT/MCT_{120} (n = 8 each; the subscripts represent respective observation period). LCT_{15}-LCT_{120} and LCT/MCT_{15}-LCT/MCT_{120} groups received Intralipid 20% or Lipovenoes 20%, respectively. Plasma and myocardial bupivacaine and triglyceride concentrations, as well as myocardial bioenergetics, were determined.

RESULTS: In experiment A, 24 rats in LCT group and 23 in LCT/MCT group achieved return of spontaneous circulation (P = 0.754); among them, 2 (8.3%) and 8 (34.8%) rats suffered a repeated asystole, respectively (P = 0.027). In experiment B, plasma and myocardial bupivacaine concentrations in LCT_{15} and LCT_{60} groups were lower than LCT/MCT_{15} and LCT/MCT_{60} groups, respectively. Furthermore, the plasma bupivacaine level in LCT/MCT_{60} group was higher than LCT/MCT_{30} group (P = 0.003).

CONCLUSIONS: LCT emulsion may be superior to LCT/MCT emulsion in treating bupivacaine-related cardiotoxicity as it was associated with fewer recurrences of asystole after resuscitation and lower myocardial bupivacaine concentrations.

- 2011, Li et al
- Reported that LCT and LCT/MCT mixture were equally effective in initial reversal of severe Bupivacaine overdose, but subsequently LCT group has better survival

WHICH LIPID EMULSION (LE)?

Table 1. *Clinical Case Reports on the use of Lipid Emulsion in Bupivacaine-related LAST*

Author	Block Type	Local Anesthetic	Symptoms of LAST: CNS	Symptoms of LAST: CV	Lipid Emulsion	Volume of Lipid Emulsion	Resolution of Symptoms
Cordell et al[19]	Axillary	Bupivacaine 0.5% (15 mL)	Seizures	VT	Intralipid 20%	100 mL bolus	Yes
Markowitz and Neal[20]	Femoral	Bupivacaine 0.5% (20 mL)	Seizures	VF	Intralipid 20%	500 mL over 30 min	Yes
McCutchen and Gerancher[21]	Femoral and Sciatic	Bupivacaine 0.5% (30 mL) and Ropivacaine 0.5% (30 mL)	Seizures	VT	Intralipid 20%	100 mL bolus, 400 mL over 15 min	Yes
Rosenblatt et al[22]	Interscalene	Bupivacaine 0.5% (20 mL) and mepivacaine 1.5% (20 mL)	Seizures	Asystole	Intralipid 20%	1.2 mL/kg bolus, 0.5 mL/kg/min infusion	Yes
Shah et al[23]	Caudal	Bupivacaine 0.25% (4 mL)	None (general anesthesia)	ST elevation, T-wave inversion, Hypotension	Intralipid 20%	2 mL/kg bolus	Yes
Smith et al[24]	Sciatic	Bupivacaine 0.5% (26 mL)	Loss of consciousness, seizures	Asystole	Intralipid 20%	3 mL/kg bolus, 0.2 mL/kg/min infusion	Yes
Spence[25]	Epidural	Bupivacaine 0.5% (10 mL)	Agitation, seizures	None	Intralipid 20%	100 mL bolus, 400 mL infusion	Yes
				PEA	Intralipid 20%	0.8 mL/kg bolus, 0.25 mL/kg/min infusion	Yes
				Torsade de pointes, VF, VT	Liposyn III 20%	250 mL infusion over 30 min	Yes
				SVT	Lipofundin 20%	2 mL/kg bolus, 0.5 mL/kg/min infusion	Yes

esthetic systemic toxicity; PEA, pulseless electrical activity; SVT, supraventricular

Table 2. *Case Reports on the use of Lipid Emulsion in Nonbupivacaine-related LAST*

Author	Block Type	Local Anesthetic	Symptoms of LAST: CNS	Symptoms of LAST: CV	Lipid Emulsion	Volume of Lipid Emulsion	Resolution of Symptoms
Aveline et al[26]	Sciatic	Lidocaine 2% and ropivacaine 0.75%, (30 mL, 1:1 mixture)	Agitation, confusion, myoclonus	None	Intralipid 20%	1.75 mL/kg bolus, repeated in 2 min	No
Charbonneau et al[27]	Axillary	Mepivacaine 2% (50 mL)	Myoclonus, confusion	None	Medialipide 20%	1.5 mL/kg bolus	Yes
Foxall et al[28]	Lumbar plexus	Levobupivacaine 0.5% (20 mL)	Seizure	Hypotension, wide QRS on EKG	Intralipid 20%	1.2 mL/kg bolus	Yes
Gnaho et al[29]	Sciatic	Ropivacaine 0.5% (20 mL)	Unconsciousness, seizure	VF	Intralipid 20%	1.6 mL/kg bolus	Yes
Litz et al[30]	Infraclavicular and axillary	Mepivacaine 1% (30 mL) and prilocaine 1% (10 mL)	Dizziness, agitation, unconsciousness	Supraventricular arrhythmias	Intralipid 20%	1.75 mL/kg bolus, 0.25 mL/kg/min infusion	Yes
Litz et al[31]	Axillary	Ropivacaine 1%, (40 mL)	Dizziness, unconsciousness, seizures	Asystole	Intralipid 20%	2 mL/kg bolus, 0.2 mL/kg/min infusion	Yes
Sonsino and Fischler[32]	Infraclavicular	Ropivacaine 0.75% (20 mL)	Seizures	Asystole	Intralipid 20%	50 mL bolus	Yes

CNS indicates central nervous system; CV, cardiovascular; EKG, electrocardiogram; LAST, local anesthetic systemic toxicity; VF, ventricular fibrillation.

WHICH LIPID EMULSION (LE)?

Optimizing the lipid emulsion will still require further comparison of different formulation

SAFETY OF ILE IN TREATING LAST

POSSIBLE COMPLICATION / ADVERSE EFFECT OF LIPID INFUSION

- Total Hb & metHb are falsely elevated
  - interference with spectrophotometric assessment
- Significant interference in:
  - albumin
  - Mg^{++} assay
  - amylase lipase
  - phosphate
  - creatinine
  - total protein
  - ALT
  - CK
  - bilirubin
- t½ hypertriglyceridemia is about 15 min, the effect should completely dissipated after a few hour

POSSIBLE COMPLICATION / ADVERSE EFFECT OF LIPID INFUSION

- No interference in:
  - Na^{++}
  - K^{+}
  - Cl^{-}
  - Ca^{++}
  - Bicarbonate
  - Urea
  - troponin assays

POSSIBLE COMPLICATION / ADVERSE EFFECT OF LIPID INFUSION

- Microbial contamination, proinflammatory effects, hepatosplenomegaly are unlikely in the treatment of LAST
- No serious clinical complication have been reported following the use of ILE in LAST

IS THERE A SAFE UPPER LIMIT OF LIPID DOSING?

IS THERE A SAFE UPPER LIMIT OF LIPID DOSING?

- Lethal dose in 50% of test animal (LD50) of Intralipid for bolus administration in rats at 48 hour to be 67.7± 10.7ml/kg
- Excellent safety profile as recommended max dose of ILE in LAST is 10-12ml/kg
- However the correct conversion of allometric scaling of this dose to a human is unknown
- Furthermore the LD50 per se cannot be readily converted to a “ maximal safe” or “lowest toxic dose”
- ??? Dosing limit for ILE

DOES IT WORK WELL FOR ALL LAs?

DOES IT WORK WELL FOR ALL LAs?

- Widely accepted for bupivacaine toxicity
- Also successful treatment in:
  - mepivacaine
  - ropivacaine
  - lidocaine
  - prilocaine
  - levo-bupivacaine

ILE IN BUPIVACAINE LAST

Table 1. *Clinical Case Reports on the use of Lipid Emulsion in Bupivacaine-related LAST*

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			CNS	CV			
Cordell et al[19]	Axillary	Bupivacaine 0.5% (15 mL)	Seizures	VT	Intralipid 20%	100 mL bolus	Yes
Markowitz and Neal[20]	Femoral	Bupivacaine 0.5% (20 mL)	Seizures	VF	Intralipid 20%	500 mL over 30 min	Yes
McCutchen and Gerancher[21]	Femoral and Sciatic	Bupivacaine 0.5% (30 mL) and Ropivacaine 0.5% (30 mL)	Seizures	VT	Intralipid 20%	100 mL bolus, 400 mL over 15 min	Yes
Rosenblatt et al[22]	Interscalene	Bupivacaine 0.5% (20 mL) and mepivacaine 1.5% (20 mL)	Seizures	Asystole	Intralipid 20%	1.2 mL/kg bolus, 0.5 mL/kg/min infusion	Yes
Shah et al[23]	Caudal	Bupivacaine 0.25% (4 mL)	None (general anesthesia)	ST elevation, T-wave inversion, Hypotension	Intralipid 20%	2 mL/kg bolus	Yes
Smith et al[24]	Sciatic	Bupivacaine 0.5% (26 mL)	Loss of consciousness, seizures	Asystole	Intralipid 20%	3 mL/kg bolus, 0.2 mL/kg/min infusion	Yes
Spence[25]	Epidural	Bupivacaine 0.5% (10 mL)	Agitation, seizures	None	Intralipid 20%	100 mL bolus, 400 mL infusion	Yes
Wong et al[17]	Epidural	Bupivacaine 0.125% (5 mL)	None (general anesthesia)	PEA	Intralipid 20%	0.8 mL/kg bolus, 0.25 mL/kg/min infusion	Yes
Warren and Weinberg[18]	Supraclavicular	Bupivacaine 0.5% (10 mL) and mepivacaine 1.5% (30 mL)	Loss of consciousness	Torsade de pointes, VF, VT	Liposyn III 20%	250 mL infusion over 30 min	Yes
Zimmer et al[12]	Epidural	Bupivacaine 0.25% (10 mL)	Agitation	SVT	Lipofundin 20%	2 mL/kg bolus, 0.5 mL/kg/min infusion	Yes

CNS indicates central nervous system; CV, cardiovascular; LAST, local anesthetic systemic toxicity; PEA, pulseless electrical activity; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

ILE IN NON BUPIVACAINE RELATED LAST

Table 2. *Case Reports on the use of Lipid Emulsion in Nonbupivacaine-related LAST*

Author	Block Type	Local Anesthetic	Symptoms of LAST		Lipid Emulsion	Volume of Lipid Emulsion	Resolution of Symptoms
			CNS	CV			
Aveline et al[26]	Sciatic	Lidocaine 2% and ropivacaine 0.75%, (30 mL, 1:1 mixture)	Agitation, confusion, myoclonus	None	Intralipid 20%	1.75 mL/kg bolus, repeated in 2 min	No
Charbonneau et al[27]	Axillary	Mepivacaine 2% (50 mL)	Myoclonus, confusion	None	Medialipide 20%	1.5 mL/kg bolus	Yes
Foxall et al[28]	Lumbar plexus	Levobupivacaine 0.5% (20 mL)	Seizure	Hypotension, wide QRS on EKG	Intralipid 20%	1.2 mL/kg bolus	Yes
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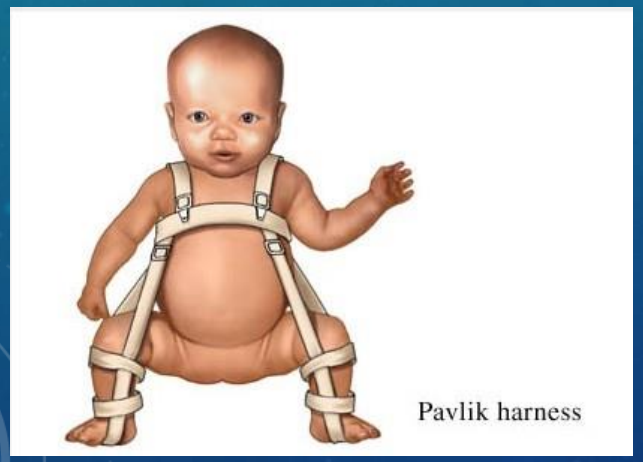
Litz et al[30]	Infraclavicular and axillary	Mepivacaine 1% (30 mL) and prilocaine 1% (10 mL)	Dizziness, agitation, unconsciousness	Supraventricular arrhythmias	Intralipid 20%	1.75 mL/kg bolus, 0.25 mL/kg/min infusion	Yes
Litz et al[31]	Axillary	Ropivacaine 1%, (40 mL)	Dizziness, unconsciousness, seizures	Asystole	Intralipid 20%	2 mL/kg bolus, 0.2 mL/kg/min infusion	Yes
Sonsino and Fischler[32]	Infraclavicular	Ropivacaine 0.75% (20 mL)	Seizures	Asystole	Intralipid 20%	50 mL bolus	Yes

CNS indicates central nervous system; CV, cardiovascular; EKG, electrocardiogram; LAST, local anesthetic systemic toxicity; VF, ventricular fibrillation.

- Aveline et al ; patient was taking carbamazepine, may caused drug interaction with LA as it bind to voltage-gated sodium channels also. And also lidocaine has low lipid solubility

DOES ILE CONFER BENEFIT IN THE PAEDIATRIC & ELDERLY POPULATION SUFFERING LAST



ILE IN PAEDIATRIC & ELDERLY PATIENT

Table 1. *Clinical Case Reports on the use of Lipid Emulsion in Bupivacaine-related LAST*

Author	Block Type	Local Anesthetic	Symptoms of LAST		Lipid Emulsion	Volume of Lipid Emulsion	Resolution of Symptoms
			CNS	CV			
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Markowitz and Neal[20]	Femoral	Bupivacaine 0.5% (20 mL)	Seizures	VF	Intralipid 20%	500 mL over 30 min	Yes
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Rosenblatt et al[22]	Interscalene	Bupivacaine 0.5% (20 mL) and mepivacaine 1.5% (20 mL)	Seizures	Asystole	Intralipid 20%	1.2 mL/kg bolus, 0.5 mL/kg/min infusion	Yes
Shah et al[23]	Caudal	Bupivacaine 0.25% (4 mL)	None (general anesthesia)	ST elevation, T-wave inversion, Hypotension	Intralipid 20%	2 mL/kg bolus	Yes
Smith et al[24]	Sciatic	Bupivacaine 0.5% (26 mL)	Loss of consciousness, seizures	Asystole	Intralipid 20%	3 mL/kg bolus, 0.2 mL/kg/min infusion	Yes
Spence[25]	Epidural	Bupivacaine 0.5% (10 mL)	Agitation, seizures	None	Intralipid 20%	100 mL bolus, 400 mL infusion	Yes
Wong et al[17]	Epidural	Bupivacaine 0.125% (5 mL)	None (general anesthesia)	PEA	Intralipid 20%	0.8 mL/kg bolus, 0.25 mL/kg/min infusion	Yes
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CNS indicates central nervous system; CV, cardiovascular; LAST, local anesthetic systemic toxicity; PEA, pulseless electrical activity; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

→ Octogenerian

→ Infant

→ Octogenerian

→ 6 yr

→ Octogenerian

OPTIMAL DOSE OF ILE IN LAST?

OPTIMAL DOSE OF ILE IN LAST

- The optimal dose is unknown!

Table 1. *Clinical Case Reports on the use of Lipid Emulsion in Bupivacaine-related LAST*

Author	Block Type	Local Anesthetic	Symptoms of LAST: CNS	Symptoms of LAST: CV	Lipid Emulsion	Volume of Lipid Emulsion	Resolution of Symptoms
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Warren and Weinberg[18]	Supraclavicular	Bupivacaine 0.5% (10 mL) and mepivacaine 1.5% (30 mL)	Loss of consciousness	Torsade de pointes, VF, VT	Liposyn III 20%	250 mL infusion over 30 min	Yes
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CNS indicates central nervous system; CV, cardiovascular; LAST, local anesthetic systemic toxicity; PEA, pulseless electrical activity; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2. *Case Reports on the use of Lipid Emulsion in Nonbupivacaine-related LAST*

	Symptoms of LAST		Lipid Emulsion	Volume of Lipid Emulsion	Resolution of Symptoms
			Intralipid 20%	1.75 mL/kg bolus, repeated in 2 min	No
			Medialipide 20%	1.5 mL/kg bolus	Yes
, wide			Intralipid 20%	1.2 mL/kg bolus	Yes
EKG			Intralipid 20%	1.6 mL/kg bolus	Yes
cular			Intralipid 20%	1.75 mL/kg bolus, 0.25 mL/kg/min infusion	Yes
ias					
			Intralipid 20%	2 mL/kg bolus, 0.2 mL/kg/min infusion	Yes
			Intralipid 20%	50 mL bolus	Yes

cal anesthetic systemic toxicity; VF, ventricular fibrillation.

DOSES OF ILE

Recommended dose of 20% Intralipid in LAST:

- 1.5ml/kg bolus over 1 min (≈100ml in 70 kg)
- followed by infusion of 0.25ml/kg/min ,by ideal body weight, (≈1000ml/hr in 70kg)
- if no respond, repeat the bolus dose up to a total of 3 boluses, 3-5 min apart, followed by increasing the infusion to 0.5ml/kg/min
- continue the infusion for roughly 10 min following the recovery of the V/S
- max dose is 10-12ml/kg, given over 30 min (≈800ml in 70 kg)

HOW DO WE INTERGRATE ILE INTO STANDARD ACLS RESUSCITATION ?

- 9 CASE REPORTS OF LAST WITH CVS TOXICITY

ILE administered late (10-20 min of ACLS)

- 4 cases
- Given a few doses of epinephrine and vasopressin
- Responded within minutes of ILE
- All patients survive

ILE administered early (2-3 min of ACLS)

- 2 cases given ILE only, no vasopressors
- 3 cases single dose of epinephrine before the ILE, no further vasopressors needed
- All patients survived

SHOULD LIPID BE USED ALONE OR IN COMBINATION WITH EPINEPHRINE AND OTHER COMPONENT OF STANDARD RESUSCITATION COCKTAILS?

- Epinephrine > 10μg /kg in conjunction with ILE

  - lesser rates of recovery of spontaneous circulation (ROSC)

  - deteriorating metabolic parameters (hyperlactatemia)

  - ↑ cardiac arrhythmogenesis

EPINEPHRINE AS CO-TREATMENT WITH ILE IN LAST

- **LI & colleague (BR J Anaesth 2012)**

  – superior outcome with epinephrine + LE compound when compared with lipid alone

- **Mauch & colleagues (Paediac Anaesth 2012)**

  - reported greatest survival (86%) with a combination of lipid and epinephrine compared with just 29% with lipid only

- **Mayr & colleagues (Anesth Analg 2008)**

  - epinephrine/Vasopressin combination was superior in achieving ROSC when compared with ILE alone

EPINEPHRINE AS CO-TREATMENT WITH ILE IN LAST

- **Weinberg G (2008 Anesthesiology) & Di Gregorio G (Crit Care Med 2009)**

  - ILE result in superior haemodynamic & metabolic recovery compared with epinephrine either alone or in combination with vasopressin

- **Hiller D, Gregorio G (Anesthesiology 2009)**

  - identical rate of ROSC when ILE was co administered with or without low-dose epinephrine, albeit, epinephrine was associated with more rapid circulation return

EPINEPHRINE AS CO-TREATMENT WITH ILE IN LAST

- **Liu & colleagus (Anesth Analg 2012)**

  - time to heart beat recovery was significantly shorter in both the lipid and lipid + epinephrine group compared to control and epinephrine alone

  - cardiac tissue bupivacaine concentration was noted to be significantly higher in the control and epinephrine treated group

EPINEPHRINE AS CO-TREATMENT WITH ILE IN LAST

- **Carreiro S & colleagues (J Med Toxcol 2013)**

  - interaction between ILE and epinephrine in animals models

  - ILE pretreatment was shown to delayed the peak effect on MAP and prolong its duration without altering the peak increase in either MAP or HR respond in rats administered iv epinephrine at 15μg/kg

  - some interaction between ILE and additional lipophilic resuscitation drugs likewise may occur potentially limiting their intended utility

EPINEPHRINE AS CO-TREATMENT WITH ILE IN LAST

- Conclusion from pre – clinical data, ILE used alone:
  - may confer equivalent resuscitation outcome
  - lesser arrhythmogenesis
  - improved post- arrest metabolic parameters
- However this will still need more greater power studies

LIMITATION IN ANIMALS STUDY

- Variation in animal models used
  - rat
  - rabbit
  - dog
  - pig (allergic to LE)
- Different resuscitation regimes
- Small sample sizes

ONGOING RESEARCH

- The optimal dose is unknown
- Use of epinephrine in cardiac arrest , in the present of ILE, is beneficial or not
- Whether ILE is associated with long –term sequelae
- ILE may be used for other intoxication treatment although the evidence is small
- ILE may have a role in ischemic-reperfusion injury

CURRENT RECOMMENDATION & PRACTICAL CONSIDERATION

- Guidelines for the use of ILE in LAST are available through:

  - ASRA

  - AAGBI (Asso. Of Anaesthetists of Great Britain and Ireland)

  - AHA

- Early ACLS/ BLS including adrenaline with immediate ILE injection in LAST

  - airway, O_2,circulation

  - seizure suppression (benzodiazepine/ STP/ propofol)

  -early ILE

  - treat arrhythmias, conduction block, hypotension & bradycardia as in ACLS

  » avoid LIDOCAINE as an anti-arrhythmic

CURRENT RECOMMENDATION & PRACTICAL CONSIDERATION

- In toxic cardiomyopathy, raising PVR with potent vasopressors can impair CO & impede resuscitation

  - therefor , vasopressin is not considered useful & epinephrine should be used in small doses (< $10\mu g/kg$)

- These guidelines will likely subject to frequent modification based on the new finding

CONCLUSION

- LAST is rare, but may be fatal
- LAST is unpredictable, but many are preventable
- The key is to recognize it early and institute appropriate management immediately
- Early ILE therapy has significant advanced management of this emergency


THANK YOU!
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