Lipid Rescue
From Bench to Bedside

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THE PLAN...

- Science of «lipid rescue»
- Safety of lipid infusions
- Current research
- Diagnosis of LAST
- What’s next

Este artículo puede ser consultado en versión completa en http://www.medigraphic.com/rma
TIMELINE OF BUPIVACAINE AND LAST

1957  BUPIVACAINE SYNTHESIZED
1970  REPORTS OF CARDIAC ARRESTS
1983  75% NO LONGER INDICATED IN OB
2006

GUY WEINBERG, M.D.

- 16 yr-old female
- Isovaleric acidemia
  — Autosomal recessive dx of leucine catabolism
    - Isovaleryl-CoA dehydrogenase deficiency
    - Carnitine deficiency
    - May sensitize heart to arrhythmias
  — Arrhythmias during axillary liposuction
    - 22 mg (0.4 mg/kg) bupivacaine
- Bupivacaine inhibits carnitine-dependent pathway

INVESTIGATION

- Measured respiration in cardiac mitochondria oxidizing lipid and non-lipid substrates
  — To see effect of bupivacaine
- Found bupivacaine inhibits key step in mitochondrial transport
- Also...
  — Pretreatment with lipid increases the dose of bupivacaine to induce asystole in rats
• Pretreatment experiment
  • 6 rats/treatment group—GA and instrumentation
  • Pretreated with 3 mL/kg/min with:
    — Saline
    — Intralipid 10%
    — Intralipid 20%
    — Intralipid 30%
• 0.75% bupivacaine 10mg/kg to 10s of asystole
• Concentrations of bupivacaine in plasma to cause arrest:
  — 12.7 mg/kg
  — 17.8 mg/kg
  — 49.8 mg/kg
  — 82.0 mg/kg

**RESUSCITATION**

• Anesthetized rats
• Bupivacaine bolus
• Ventilation 100% O₂
• Bolus of:
  — Saline
  — 30% lipid
  — Followed by infusions
• Compressions PRN
• Survival
  — HR > 100 bpm
  — SBP > 60 mmHg
• Lipid shifts dose-response curve to bupivacaine–induced asystole
  — LD50 from 12.5 to 18.5 mg/kg

**LIPID INFUSIONS ARE:**

• Emulsion in water:
  — Soybean oil
    - (predominantly neutral triglycerides)
    - Made isotonic with glycerin
  — Egg lecithin
    - The emulsifying agent
    - NO preservatives
• Particles 0.5 μm in diameter
• In blood these fat droplets form a lipid compartment
• But not just a lipid sink…

• 12 hounds (22-26 kg) under GA
• Bupivacaine 10 mg/kg injected
• 10 minutes internal cardiac massage
• 20% lipid -or- saline
• 4mL/kg bolus then 0.5 mL/kg/min infusion
• 100 versus 0% survival
POTENTIAL MECHANISMS OF ACTION

• «Lipid sink»
  — Sequestration of toxins of high lipophilicity
  — Bupiv lipid: aqueous partition coefficient = 11.9:1
• Cytoprotection
  — Akt (protein kinase B) activation
• Competition
  — Inhibition of ion channel binding
• Pharmacokinetics
  — Shunting to sequestering organs
• Inotropic/ionotropic
  — Activation of calcium currents
• Metabolic
  — Reverses the inhibitory effect of bupivacaine on lipid-based mitochondrial respiration

SAFETY OF LIPID INFUSIONS - LD 50 IN RATS

- 20% lipid (20, 40, 60 or 80 mL/kg) or saline
- Over 30 minutes
- Dixon «up-and-down» method
- Recovered and observed for 48 hours
- Euthanized and organs harvested
- Three additional rats given 60 mL/kg
  — Euthanized at 1, 4, 24 hours
  — To identify progression of organ damage

LD₅₀ = 67.72 ± 10.69 ML/KG

- Three animals died
  — 2 at 80 mL/kg, 1 at 60 mL/kg
  — No specific etiology
- No CNS excitation/focal defects/motor abnormalities
  — Lethargy after receiving 80 mL/kg
- No CV changes
- Triglycerides markedly ↑ after all infusions
  — All returned to baseline by 48 hours
- Microabnormalities in lung and liver at 60/80 mL/kg
  — Histopathology worse at 1 hour than 4 and 24 hours
- Supports safety of lipid infusion at current doses

OTHER CONCERNS

- Pulmonary comps—
  — Pts w/nl lung or pulm compromise without ARDS do not demonstrate ↓ oxygenation or pulmonary vascular changes
  — Pulmonary changes with ARDS 2° to:
    — Enhanced inflammation
    — Transient

Large lipid doses will interfere with laboratory studies and have caused chemical hyperamylasemia without symptoms of pancreatitis

Are all formulations of lipid equal?

- Long chain triglyceride (LCT) emulsions more efficient than LCT/medium chain triglyceride (MCT) formulations to bind long-acting LAs
  — Study in vitro

Model of anesthetized and ventilated piglets
- LCT and LCT/MCT both reversed effects
  — QRS duration
  — Atrial-His
  — PQ intervals

Caution with extrapolations to humans

BACK TO THE STORY...

A 58 year-old male presents for shoulder surgery

- H/o coronary artery bypass
- Has angina
- ECG
  — Right bundle branch block
  — Left anterior hemiblock
  — Old anterior wall MI
- Meds
  — NTG PRN
  — Lisinopril
  — Atenolol
  — Clopidogrel
  — Aspirin
- Refused further cardiac work-up

REATIONS

- Contamination
- Direct reactions
  — Pyogenic
    - 10-20 min post-infusion
    - Nausea, vomiting, chills fever, headache chest pain, dyspnea, cyanosis (< 1%)
  — Thrombophlebitis
- Allergy
  — Soybean oil
THE BLOCK

- ASA monitors, O₂ via nc
  - Midazolam 2 mg
  - Fentanyl 50 μg
- ISB→ stimulation at .34 mA
  - Negative aspiration
- Agents
  - Mepivacaine 300 mg
  - Bupivacaine 100 mg
  - In 5 cm³ aliquots with aspiration between

AND THEN...

- 30 seconds after injection
  - Tonic-clonic seizure
  - O₂ via self-inflating resuscitation bag
  - Propofol 50 mg
- 90 seconds later
  - Seizure restarts
  - Propofol 100 mg
  - V tach→ V fib→ Asystole
- Endotracheal intubation and CPR

RESUSCITATION

- Full ACLS
  - (At least 6 attendings and 1 resident)
- Central line/arterial line attempts
- Plans for cardiopulmonary bypass

OUR INTERVENTION

- 100 cm³ of 20% lipid infusion IV
- Continued CPR
- Single sinus beat
  - Epinephrine
  - Atropine
- Return to sinus rhythm
- No neurologic sequelae
- (ISB block)

TOO SOON TO CELEBRATE?

QUESTIONS

- Adequacy of cardiac work-up
- Use of propofol to manage seizures
- Appropriate use of defibrillation
- Timeliness of initiation of mechanical ventilation
- Possibility of spontaneous recovery
- Choice of local anesthetic
  - «Retrobupivacaine»

CASE REPORT

Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion*

R. J. Uitz, M. Poppy, S. K. Stiehr and T. Koch
Department of Anesthesiology and Intensive Care Medicine, Erasmus Univ. Sch. Med., Rotterdam, The Netherlands.

CASE REPORT

Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid®

I. Fecské, T. K. McCauley, J. Lamb, J. G. Hardman and N. M. Bedforth
Fellow in Regional Anesthesia, J. Spinal Nerve, Consultant Anesthesiologist, Department of Anesthesiology, Associate Professor and Reader in Anaesthetics, University Department of Anaesthetics, Queen’s Medical Centre, Nottingham, NG7 2UH, UK.

SIMULATION EDUCATION IN ANESTHESIA TRAINING: A CASE REPORT OF SUCCESSFUL RESUSCITATION OF BUPIVACAINE-INDUCED CARDIAC ARREST LINKED TO RECENT SIMULATION TRAINING

Phillip M. Smith, M.D., Ph.D.
Simulation training is rapidly becoming an integral element of the education curriculum of anesthesia residency programs. We report a case of successful resuscitation of a patient with bupivacaine-induced cardiac arrest. This case illustrates the importance of simulation training in improving the ability to recognize and manage cardiac arrest.

INTRAVENTURAL LIPID INFUSION IN THE SUCCESSFUL RESUSCITATION OF LOCAL ANESTHETIC-INDUCED CARDIOVASCULAR COLLAPSE AFTER SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

Julie A. Warren, M.D.
R. Brian Thomas, M.D.
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We describe a case of successful resuscitation with an IV lipid infusion of a local anesthetic-induced cardiovascular toxicity due to a supraclavicular brachial plexus block with neopentylglycol and bupivacaine. This toxicity can be rescued with rapid recognition and aggressive resuscitation.
SCIATIC BLOCK

- 83 yr-old 75 kg, TKA with GA plus:
  - Continuous FNB
  - Single-injection sciatic block
- Block with NS technique
- During injection of bupivacaine 130 mg
  - LOC
  - Tonic-clonic seizure
  - Pulselessness

LIPID EMULSION 3 ML/KG

Baseline ECG
ECG During Resuscitation
ECG During Seizure
Wide Complex Tachycardia with pulse
Asystole
Narrowing Pulsatile Tachyarrhythmia


HOW TO INCORPORATE LIPID INTO RESUSCITATION?

RESUSCITATION WITH LIPID
VERSUS EPI
VERSUS SALINE

- Rats + isoflurane + bupivacaine 20 mg/kg
- 100% O2 + chest compressions
- Boluses of resuscitation drugs at 2.5 and 5 min
  - 30% lipid
  - Saline
  - Epinephrine 30 μg/kg
- Continuous ECG, arterial pressure
- RPP, pH, lactate, SCVPO2

All metrics improved more with lipid
80% rats with Epi had pulmonary edema
100% w/epi had ectopy
Epi might worsen:
- Tissue perfusion
- Cardiac output
- O2 delivery
Epi exerts direct metabolic effects that ↑ lactate
Quality of recovery after epi no better than controls
- May even be worse
**EPINEPHRINE IMPAIRS RESUSCITATION**

- 30 rats/6 groups
- Bupivacaine 20 mg/kg
- All tx at 3 minutes
- 30% lipid + epi
- Lipid alone had slower but more sustained recovery
- Epi > 10 μg/kg improved initial return but not sustainable
- Pulmonary edema

**IS HYPERADRENERGIC STIMULATION DETRIMENTAL?**

- Epinephrine
  - Is arrhythmogenic
  - ↑ myocardial oxygen demand
  - ↓ subendocardial perfusion
  - Causes pulmonary edema
- LA cardiac toxicity ↓ contractility, worsened by acidosis
- Repeat boluses may aggravate toxicity
  - By causing intense vasoconstriction
  - Increasing lactate

**VASOPRESSIN + EPI ↑ CPP MORE THAN LIPID IN A PORCINE MODEL OF BUPI-INDUCED ARREST**

- 10 adult pigs with GETA
- 5 mg/kg bupivacaine
- CPR begun 1 minute post-arrest x 2 minutes
- Randomized
  - 4 mL/kg lipid → 0.5 mL/kg/min
  - Vasopression + epi (0.4/45, 0.4/45, 0.8/200 U/kg and μg/kg) every 5 minutes
- 5 in the vasopressor group survives, 0 in lipid

Compliment activation-related pseudoallergy (CARPA)...

Authors of 16 papers who did studies 1991-2011 contacted...

 Are pigs an appropriate model?

DELAYED RESUSCITATION

32 rats with bupivacaine arrest (30 mg/kg)

BLS x 10 minutes

Treatment

- Saline-1 mL/kg @ 1, 3, 5 min then 5 mL/kg at 10 min and 0.5 mL/kg/min
- Epi-10 μg/kg @ 1, 3, 5, 10 min then q 3 min to RPP < 20% baseline
- Lipid-1 mL/kg @ 1, 3, 5 min then 5 mL/kg at 10 min and 0.5 mL/kg/min
- Lipid+epi-same as lipid but epi 10 μg/kg @ 10 min (12, 15 if needed)

Results

- Lipid+epi had marked improvement in hemodynamics to lipid at 25 min
  - CPP higher
  - Myocardial bupivacaine content lower
- Lipid alone (3/8 survived)
  - Higher PO₂
  - Less severe acidosis

LIPID-ONLY RATS HAD LESS INTERSTITIAL PULMONARY EDEMA

Wet-to-dry lung weight ratio

NS (P>0.05)
ASRA RECOMMENDS

REDUCING INDIVIDUAL DOSES OF EPINEPHRINE TO < 1 μG/KG

INTELLECTUAL LEAPS...

AMELIORATION OF LIPID SOLUBLE DRUG TOXIDROMES

OVERDOSE IN THE ED

• 17 yr-old female
• Seizure activity and cardiovascular collapse
  — 7.95 g bupropion (Wellbutrin XL)
  - Dopamine, norepi and serotonin-reuptake inhibitor
  — 4 g lamotrigine (Lamictal)
  - Blocks voltage-dependent sodium channels
• > 10 hours post ingestion cardiovascular collapse
• 100 mL bolus 20% lipid emulsion
• 1 minute later sustainable pulse

WHERE ARE WE NOW?

**Other Therapies**

Case reports have suggested that in patients who remain critically hypotensive despite maximal vasopressor therapy, specific interventions using intra-aortic balloon counterpulsation, ventricular assist devices, and extracorporeal membrane oxygenation or other extra corporeal life support (ECLS) devices may be lifesaving.\(^{272-274}\) While evidence remains weak, at least two human case reports indicate a possible benefit from lipid emulsion infusion for overdose by \(\beta\)-blockers.\(^{275,276}\) Animal studies are mixed.\(^{277-280}\) Because this area of therapy is rapidly evolving,\(^{281-283}\) prompt consultation with a medical toxicologist or other specialists with up-to-date knowledge is recommended when managing treatment-refractory hypotension from \(\beta\)-blocker overdose.

**Local Anesthetic Toxicity**

Inadvertent intravascular administration of local anesthetics, such as bupivacaine, mepivacaine, or lidocaine, can produce refractory seizures and rapid cardiovascular collapse leading to cardiac arrest. Clinical case reports\(^{284-285}\) and controlled animal studies\(^{296-300}\) have suggested that rapid IV infusion of lipids may reverse this toxicity either by redistributing the local anesthetic away from its site of action or by augmenting metabolic pathways within the cardiac myocyte.

Case reports have shown return of spontaneous circulation in patients with prolonged cardiac arrest unresponsive to standard ACLS measures,\(^{361,362}\) suggesting a role for administration of IV lipids during cardiac arrest. Although ideal dosing has not been determined, because dosage varied across all studies, it may be reasonable to consider 1.5 mL/kg of 20% long-chain fatty acid emulsion as an initial bolus, repeated every 5 minutes until cardiovascular stability is restored (Class Iib, LOE C).\(^{363}\) After the patient is stabilized, some papers suggest a maintenance infusion of 0.25 mL/kg per minute for at least 30 to 60 minutes. A maximum cumulative dose of 12 mL/kg has been proposed.\(^{364}\)

Some animal data suggest that lipid infusion alone may be more effective than standard doses of epinephrine or vasopressin.\(^{357,363}\) Although there is limited evidence to change routine care for severe cardiotoxicity, several professional societies advocate protocolized clinical use.\(^{364-366}\) Because this is a rapidly evolving clinical area,\(^{367,368}\) prompt consultation with a medical toxicologist, anesthesiologist, or other specialist with up-to-date knowledge is strongly recommended.
**Timing of Onset of Symptoms, N = 77**

- <1 minute: 60%
- 1-5 minutes: 20%
- 5-10 minutes: 10%
- >10 minutes: 10%

**Spectrum of Presenting Signs, N = 93**

- CNS: 45%
- CNS & CV: 44%
- CV: 11%

**Spectrum of Cardiac Signs**

- Tachycardia: 14%
- Hypotension: 18%
- Bradycardia/Asystole: 31%
- Ventricular Ectopy: 6%
- Wide Complex: 14%
- ST Change, Pain, Dyspnea, HTN: 10%

**Recommendations for Diagnosing LAST**

- Progression of subjective symptoms
  - Vigilant
- Timing is variable
  - < 1 minute - IV injection with direct access to brain
  - 1-5 minutes - partial IV injection/slow circ time/delayed absorption
  - > 15 minutes - consider monitoring for 30 min
- Heightened vigilance
  - Underlying disease
  - Extremities of age
- Have LOW threshold for considering dx of LAST with atypical symptoms after receiving more than minimal dose

**Prevention**

- Use the lowest effective dose of local anesthetic (dose = volume x concentration).
- Particularly with fixed needle techniques, incrementally pause 15-30 seconds between injections.
- Aspirate before each injection, but recognize that aspiration has a 2% false negative rate.
- Intravenous markers are highly recommended. Only epinephrine (1015 mg per test dose) or fentanyl (100 mg in laboring patients) have been proven effective for this purpose.
- Ultrasonographic guidance reduces the frequency of accidental vascular puncture, but studies are conflicting regarding its ability to actually decrease AIS1 events. Ultrasound guidance should not be considered a substitute for other preventative measures.
- Patients receiving potentially toxic doses of local anesthetic should be monitored for at least 30 minutes after injection.

WHAT’S ON THE HORIZON?

- Dissemination of guidelines for the treatment of LAST
- Studies elucidating the role of epinephrine/vasopressors in resuscitation needed with attention to:
  — Experimental design
  — Endpoints
- The development of anionic pegylated particles with increased surface area that may be specific LA antidotes