Outpatient LAST and the Discovery of Lipid Resuscitation



SAMBA 2024 Frontier Lecture: Friday May 3 Savannah, GA.

Guy Weinberg, MD Professor of Anesthesiology University of Illinois, Chicago @lipidguy he/him/his



Outpatient • Office Based • Non-Operating Room

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Disclosures

- I have the following financial interests or conflicts to disclose:
 - ResQ Pharma, Inc
 - Officer and Shareholder
 - Will discuss off-label use of FDA-approved medication



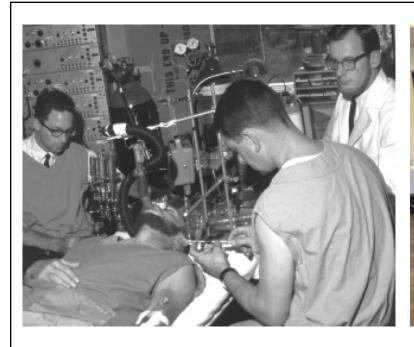


Objectives

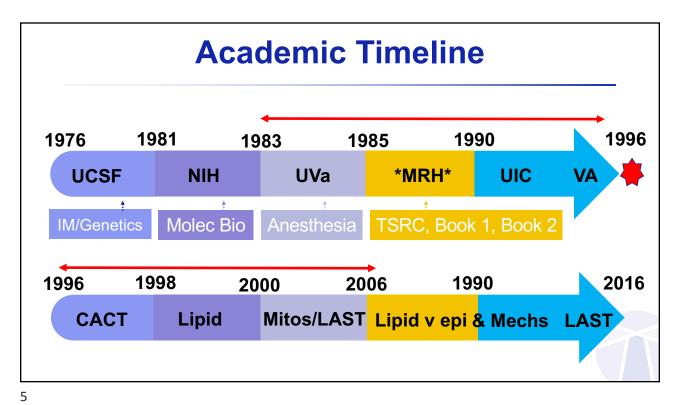
After this lecture, participants will be able to:

- Employ methods to mitigate the risk of LAST
- Explain mechanisms of lipid resuscitation
- Relate an example of translational research in anesthesiology

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UCSF 1976-1979 (IM→Med Genetics)

Bestler

Lloyd Hollander "Holly" Smith

Hemochromatosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Slegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

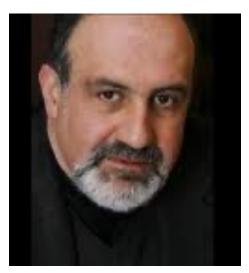
DR. SMITH: * The topic for discussion at Medical Grand Rounds today will be that of hemochromatosis. The case summary will be given by Dr. Guy Weinberg.

DR. WEINBERG: The patient is a 43-year-old white man who presented in the fall of last year to the Metabolic Clinic with the chief complaint in impotence. Five years ago the patient noted the onset of difficulty of achieving and maintaining an erection, as well as a reduced sex drive.



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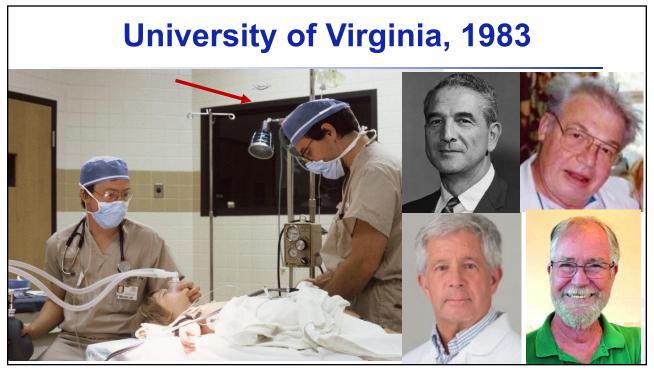
Black Swan



Black Swans: rare high-impact events account for many major scientific discoveries – Nassim Taleb, adapted from Wikipedia

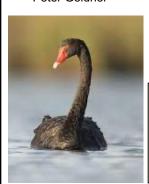








Peter Geldner



Index Case, 1996

Case Reports

Malignant Ventricular Dysrhythmias in a Patient with Isovaleric Acidemia Receiving General and Local Anesthesia for Suction Lipectomy

Journal of Clinical Anesthesia 9:668-670, 1997

Guy L. Weinberg, MD,* Charles E. Laurito, MD,† Peter Geldner, MD,‡ Bernard H. Pygon, MD,* Barbara K. Burton, MD§

Department of Anesthesiology, University of Illinois College of Medicine, Chicago, IL

- 20yo, bupivacaine 22mg, SQ.
- 3RD degree block, VT
- Severe carnitine deficiency



Bud Pygon



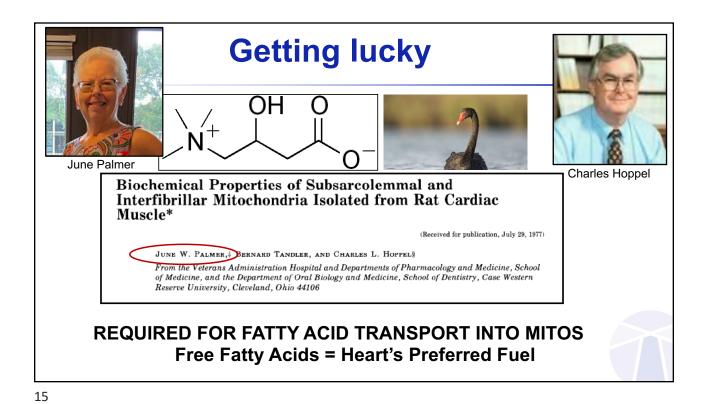
Barbara Burton

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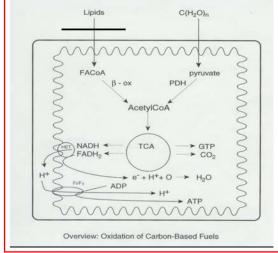
Is There a Carnitine Connection?

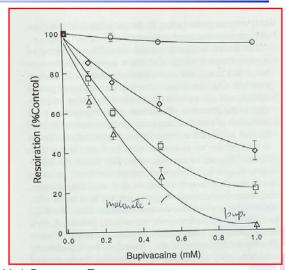
- Does carnitine deficiency predispose to LAST?
- Is carnitine linked to bupivacaine toxicity?
- Does bupivacaine interfere with carnitine?
- What does carnitine do????





Bupivacaine Inhibits Acylcarnitine Transport





Weinberg, G, Palmer J, VadeBoncouer, T and Hoppel, C. Anesthesiology 2000

Carnitine-Deficient Animal

- Carnitine deficient rat: no luck
- PB Corr says fatty acyl-carnitines = arrhythmias
- So my reasoning was....

IF BUPIVACAINE BLOCKS FATTY ACID MITO UPTAKE, INCREASING CELLULAR FATTY ACIDS SHOULD WORSEN TOXICITY, BUT NO...

THE OPPOSITE OCCURS!

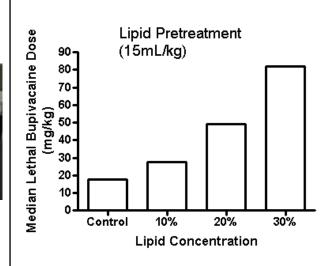


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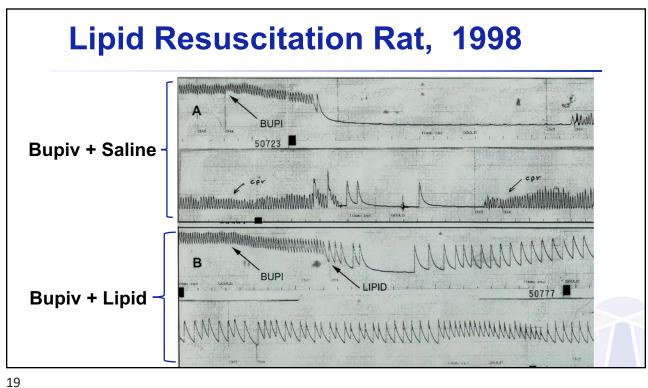
Lipid Pretreatment Protects from LAST

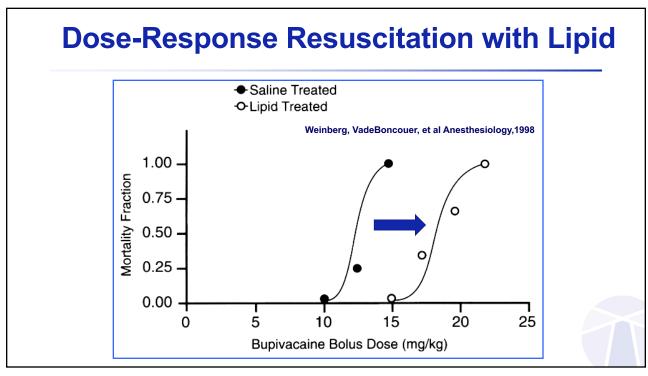


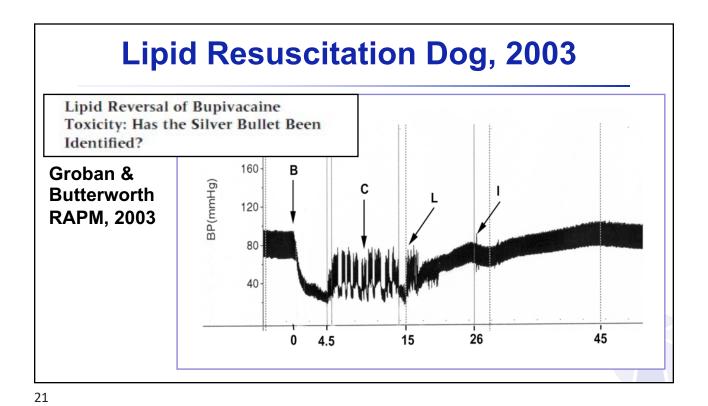
David Visintine

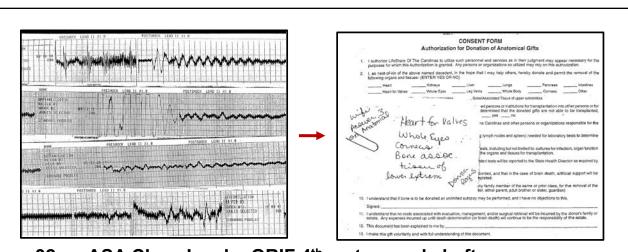












- 32 yo ASA Class I male; ORIF 4th metacarpal shaft
- Trans-arterial axillary block with 40mL 0.5% ROPIVACAINE with epi
- · Intercostal brachialis, 5mL
- General Tonic-Clonic Seizure -> bradycardia --> V Fib
- Code Blue: intubation, ACLS protocol X 2 hour

Clinical Translation, 2006

Anesthesiology 2006; 105:217-8

© 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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

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

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

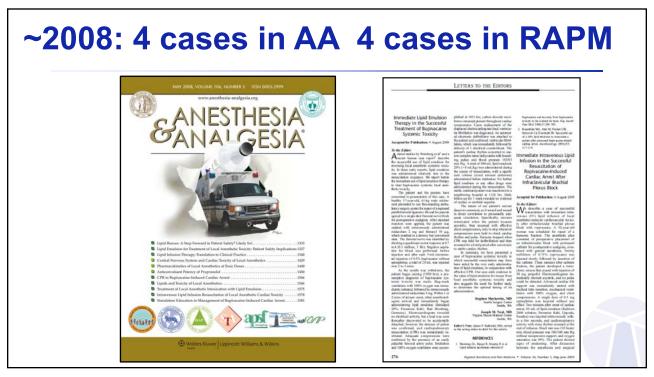


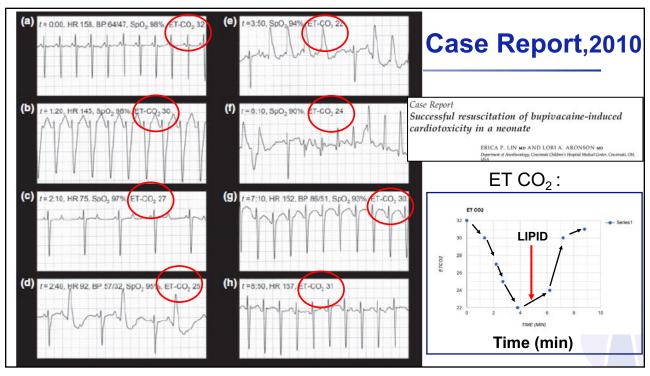
Meg Rosenblatt saved the day



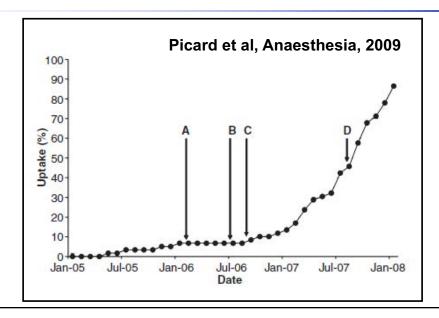
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More Case Reports Follow Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion* J. Litz, M. Popp, S. N. Stehr and T. Ko Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid® Dr. Rainer Litz Kardio- und neurotoxische Nebenwirkungen nach akzidenteller intravasaler Bupivacainapplikation Anesthesiology 2007; 107:516-7 Copyright © 2007, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc. Lipid Reversal of Central Nervous System Symptoms of Budivacaine Toxicity Andrew G. Spence, F.R.C.A., King Edward VII Memorial Hospital, Hamilton, Bermuda. aspence@transact.bm



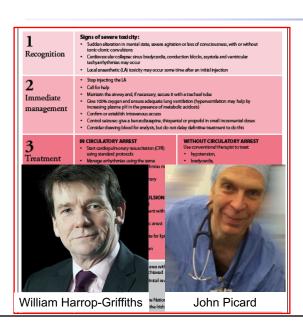


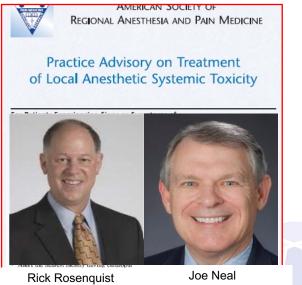
Lipid in London Hospitals, 2009

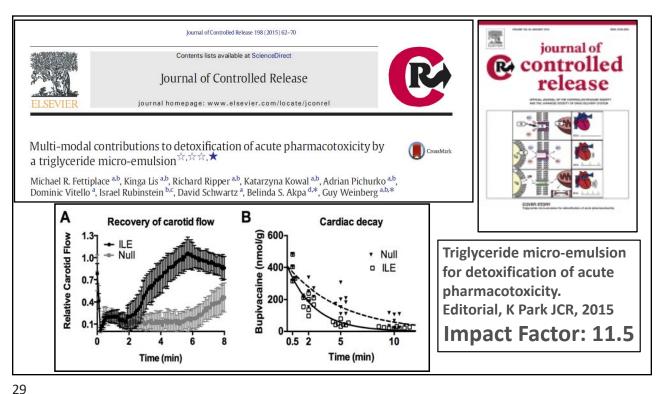


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AAGBI & ASRA LAST Advisories, 2010







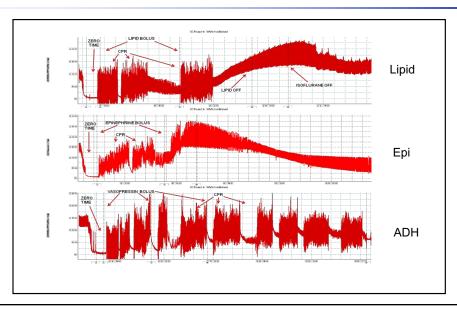
Lipid Accelerates LA Redistribution

- Partitioning + Inotropy = Redistribution
- Primary effect is pharmacokinetic
- PK effect is quick & dynamic (shuttle) not static (sink)
- Other effects occur, too: cytoprotection (RISK, Akt)

A reproducible PK effect

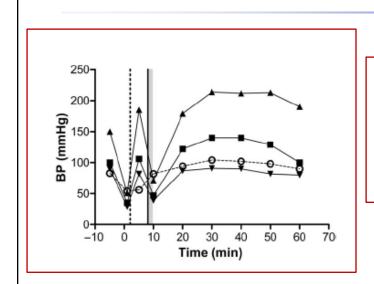


Lipid vs Pressors in ACLS for LAST



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Same Effect in the Clinical Setting



EMA

Toxicology

Successful resuscitation from bupivacaine-induced cardiovascular collapse with intravenous lipid emulsion following femoral nerve block in an emergency department

Martyn Harvey,¹ Grant Cave,² Giles Chanwai¹ and Tonia Nicholson¹ ¹Walkato Hospital, Hamilton and ³Hutt Hospital, Lower Hutt, New Zealand

Historical Recognition of LAST

Mayer E. The Toxic Effects Following the Use of Local Anesthetics. AMA, 1924.
43 cases of fatal toxicity involving cocaine or procaine

Volume 51, No. 4

October 1979

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Anesthesiology 51:285-287, 1979 **Editorial Views**

Cardiac Arrest Following Regional Anesthesia with Etidocaine or Bupivacaine

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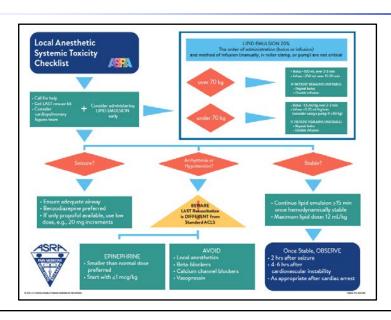
ASRA Working Group, 2022

Overarching Theme: Improving Patient Safety

- Members:
- Guy Weinberg, Chair
- Joe Neal, Co-Chair
- Michael Barrington
- Marina Gitman
- Michael Fettiplace

- Clinical:
- presentation
- epidemiology
- Risk Reduction:
- susceptible patients
- system vulnerabilities
- Treatment:
- simple, unambiguous
- cognitive aids
- **Education:**
- beyond anesthesiologists

ASRA LAST Advisory



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Rate of LAST: Rare....Or Not?

Frequency Estimates Since Mulroy, 2002 (rate = events per 10,000)

• Auroy 2002	1.4
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Orebaugh 2012 11 v 0/9096 with US

• Sites 2012 0.8 with ultrasound guidance

Barrington 2014 8 Odds Ratio 0.2 for US

Heinonen 2015 3.6 after eliminating epidurals

• Morwald 2017 18

• Rubin 2018 18

Cardiac History in Reports of Lipid Rescue from LA Toxicity
= Susceptible Groups:

Rosenblatt: prior MI, RBBB and LAHB, angina

Litz I: LABB, Stokes attacks, MVR, TVR

Warren: S/P MI, RBBB, HTN

Foxall: stable angina, QwV1-3, PAC

Litz II: CAD, MVR

Smith: S/P CABG, 2 stents

Note the unintended benefits of LipidRescue Resuscitation: More reports; clearer definition of clinical phenotype of LA toxicity. More insights into underlying mechanism and difference from lab models

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Known Susceptible Populations:

- <6 months (PRAN) = >6X increase (Polaner)
- Elderly, Frail
- Sarcopenia
- Cardiac Dz
- Na Channel-blocker
- Mitochondrial Myopathy
- NB: SMALL PATIENTS AT GREATER RISK

Most Recent Update on Susceptibility

Local anesthetic dosing and toxicity of adult truncal catheters: a narrative review of published practice

Brittani Bungart , 1,2 Lana Joudeh, 1,2 Michael Fettiplace , 1,2 Bungart B, et al. Reg Anesth Pain Med 2023;0:1–14

Box 1 Risk factors for local anesthetic systemic toxicity identified in catheters

Low weight

High weight-based dose

- ⇒ Multiple/bilateral catheters.
- ⇒ Prolonged duration (>72 hours).
- ⇒ Breakthrough doses.

Hypoalbuminemia

Albumin displacing drugs (amitriptyline). Cardiac surgery/ischemic heart disease.

Liver failure/resection.

Cytochrome P450 inhibiting medications.

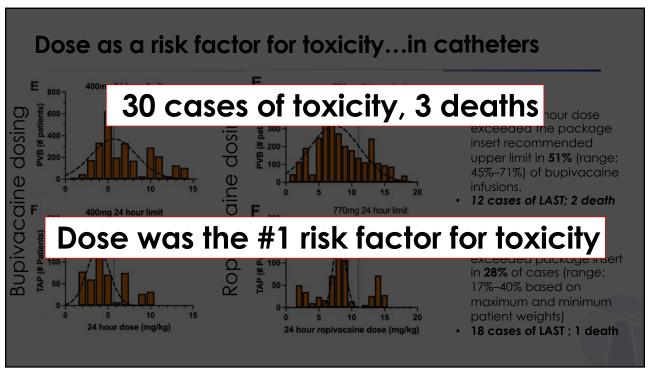
Conclusion and remaining questions

In conclusion, we investigated the use of bupivacaine and ropivacaine in PVB and TAP catheters across the literature and found frequent use of doses in excess of the package insert upper limit recommendations. We also identified cumulative dose in adult patients as a consistent risk factor for toxicity, contrary to prior meta-analysis⁶ and expert opinion. 45

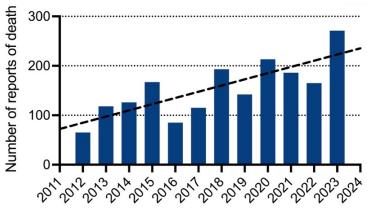
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Reports of local anesthetic associated death 2012-2023 increased approximately 15% per year relative to baseline level in 2011 (Fit line with intercept of y=80 at 2011 and slope of 12.55 reports per year, $R^2 = 0.62$)



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LAST: Evolving Clinical Context

Non-anesthesia providers: ~50%

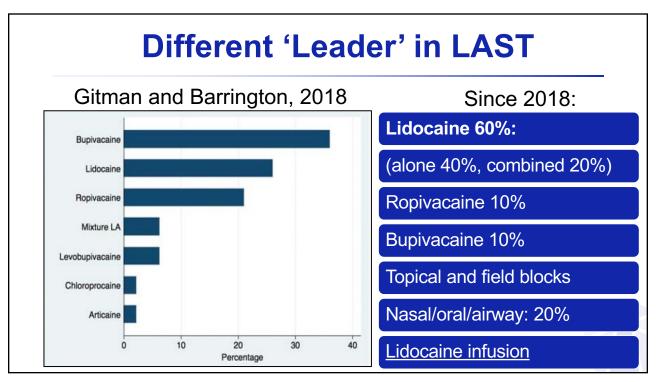
Out of hospital: 20%

Out of OR: 30%

Delayed >10min (50%) or CV 1st

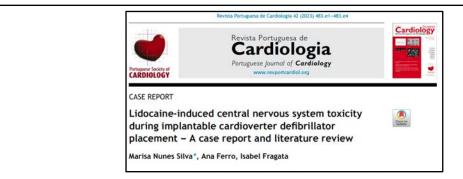
And maybe the biggest surprise.....





block	drug	dose	timing	comment	Dr	result
fem	bup	200	Immed	.675%	A	Died
SQ	Bup/lid	220,450	30m	IHR	s	Died
SQ Klein's	Bup/lid	70, 880	30m	Cocaine; phentermine	S	Survived impaired
SQ	bup	100	<10m	wrist fracture	S	Died
SQ	bup	50	10m	lipoma	S	Died
SQ Klein's	bup	22	10m	Cn def	S	Recov
caudal	bup	25 (2/k)	Immed	infant	Α	Recov
axillary	rop	200	immed	transart	Α	Died

Lidocaine Toxicity and (over)Dosing									
Age	Weight (kg)	Dose (mg) Plain	· •		Provider	ILE			
11mo	8.5	"Copious"	Topical	Delayed	Parent	No			
48y	79	100	ESP	Immediate	Anesthesiologist	No			
42y	57	330	Interscalene + Field	Immediate	Anesthesiologist	Yes			
35y	73	2,3,4 mg/min 7136 mg total 226/hr x 31.5hrs	Intravenous	Delayed	Anesthesiologist	No			
48y	67	200	Field	Delayed	Surgeon	Yes			
22y	56	600	Field	Delayed	Surgeon	Yes			
60y	58	800	Posterior tibial	Immediate	Anesthesiologist	Yes/No			
47y	64	800	Field	Delayed	Surgeon	Yes			
53y	37	600	Field		Cardiologist	Yes			
5у		1200	Topical	Delayed	Parent	Yes			
7y		800	Topical	Delayed	Parent	Yes			



53yo female, dilated cardiomyopathy, HFrEF, elective ICD.

37 kg, 85/40 mmHg, 200 mg lidocaine for local anesthesia. Pain →

400 mg more (total,16mg/kg). Shortly after, LOC, GCS 3. Epi, no effect. Anesthesiologist called to evaluate. 20% lipid emulsion 1.5 mL/kg bolus + infusion @ 0.25 mg/kg/min. Neuro-status improved to GCS 10, regained full consciousness.

Systems Can Mitigate Risk of LAST

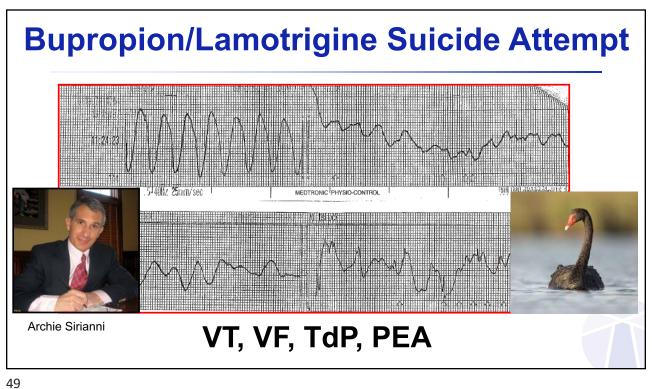
- ID high-risk patients
- Checklist: pre-block and during LAST
- Timeout: dose limit, risks

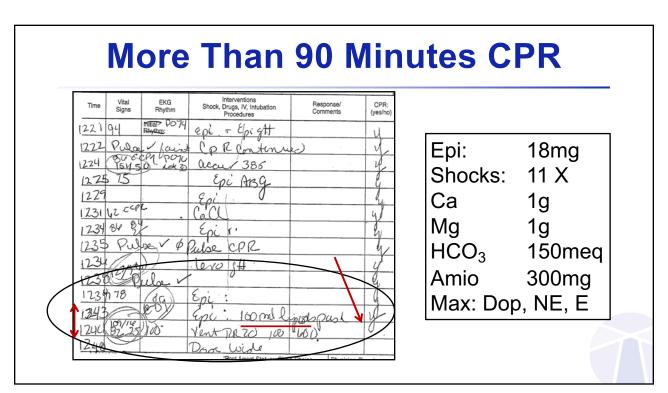
ABOVE ALL, USE COMMON SENSE!!!!

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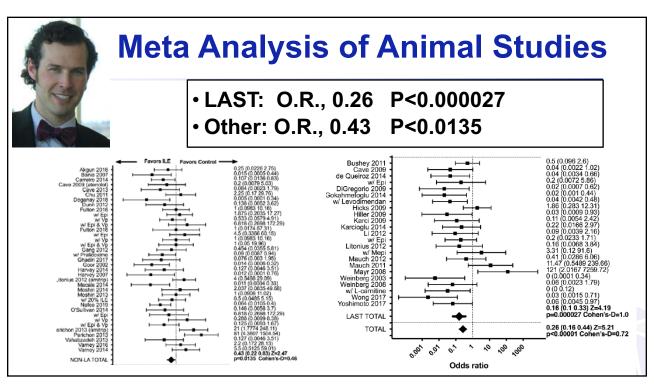
Consider Systems Refinements that Could Reduce Risk of LAST In Your Institution or Facility

- Who does the blocks?
- Who documents (time, aspiration, dosing)
- Who supervises blocks?
- Is monitoring sufficient?
- USGRA...but this isn't a panacea
- Who monitors patients after the block
- Are there contraindications to PNB?
- Timeouts....including weight, med hx
- Is there a weight-based dosing limit?
- Standard formulation of LA?

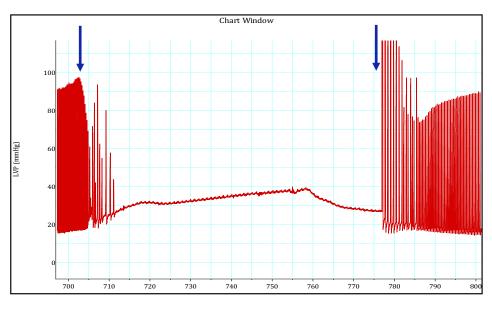




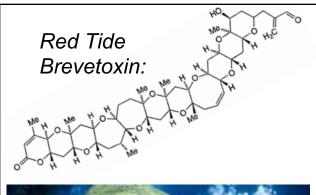




Simplest Possible Demonstration, for LAST



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Use of intravenous lipid emulsion therapy as a novel treatment for brevetoxicosis in sea turtles.

Perrault, Barron, Malinowski, Milton and Manire Nature, Scientific Reports. (2021) 11:2416

...plasma brevetoxins declined faster compared to turtles that received only SSC; survival rate was 94% (17/18), which is significantly higher than standard supportive care (47%; 46/99). Nearly all symptoms were eliminated within 48 h, whereas using SSC, symptom elimination could take up to seven days.

A Career Path Is Not a Straight Line

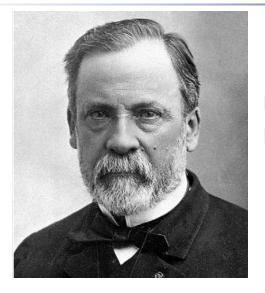


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"Chance favors the prepared mind"

- Louis Pasteur, 1854

Patience Luck



Look for the black swan Keep asking, 'Why'?









Thank you!

