What happens when my patient gets too much local anesthetic?

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Disclosure – I am the Chair of the Safety Monitoring Committee for Adynxx, which will have no influence on this lecture

Objectives

- **Objectives**:
  - Present basic local anesthetic pharmacology
  - Define LAST as to classic signs & symptoms
  - Present the currently recommended treatment of Local Anesthetic Systemic Toxicity (LAST)

Goals of clinical use of LAs

- Right volume plus the ……..
- Right concentration to……..
- Accomplish the clinical task and achieve the expected clinical result (*anesthesia* **vs** *analgesia*) but …….
- Do not add undue risk

Problems with conventional doses

- The set doses are NOT evidence-based
- Based on extrapolations from animal studies and …….
- Recommendations from the manufacturers and ……
- Modifications per case reports, etc

- Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of LAs: A multifactorial concept. RAPM 2004;29(6):564-575

Tucker & Mather in Cousin's and Bridenbaugh's textbook (1998)

- Writing about the relationship between [plasma] after IV admin in regards to CNS toxicity….
- Table values refer to the **"mythical average subject"**
- **Influenced by** whether measuring plasma or blood, total or unbound drug, ionized or *un*-ionized form, enantiomers, active drug metabolites, & the rate of admin of the drug (ie., allowing time for equilibration)

Practice changes making the old tables/charts less relevant

- Less use of large, single doses of LAs
- More repeated injections or continuous infusions with incremental aspiration and dosing injections
- Adjuvant drug use – epinephrine, clonidine, opioids, dexamethasone
- Ultrasound

Local Anesthetics

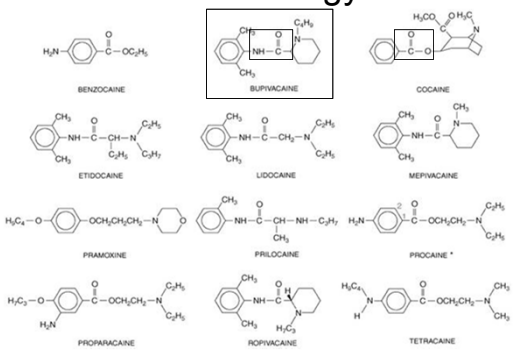
Esters

- Cocaine
- Procaine
- Chloroprocaine
- Tetracaine
- Benzocaine

Amides

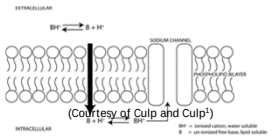
- Bupivacaine
- Etidocaine
- Levobupivacaine
- Lidocaine
- Mepivacaine
- Prilocaine
- Ropivacaine
- ((the 2 i's Rule))

Pharmacology



LA Mechanism of Action

- LAs reversibly block voltage-gated sodium channels on axons.
- The gate itself is on the intracellular side of the membrane and therefore the LA must traverse the hydrophobic portion.
- The weak base must dissociate from the hydrogen proton in order to cross the membrane, and then re-form into the cationic molecule in order to exert its effect on the sodium channel.



(Courtesy of Culp and Culp[5])

LA Toxicity: Mechanism of Action

- Once a local anesthetic reversibly binds the voltage-gated *sodium* channel, how long it stays bound and is potentially toxic are based on *plasma concentration*, which is determined by several different factors:
  - pKa, lipid solubility, and protein binding.

Pharmacological properties of local anaesthetic agents

Local anaesthetic	Linkage	pK_a	Partition coefficient Heptane buffer	Protein binding (%)	Recommended maximum adult dose (mg) Without epinephrine	With epinephrine
Cocaine	Ester	8.7		98	100	–
Bupivacaine	Amide	8.1	27.5	96	150	150
Etidocaine	Amide	7.7	800	94	–	–
Levobupivacaine	Amide	8.1	27.5	95	150	150
Lidocaine	Amide	7.9	2.9	64	200	500
Mepivacaine	Amide	7.8	21	77	350	500
Prilocaine	Amide	7.9	0.9	55	600	600 (felypressin)
Ropivacaine	Amide	8.1	6.1	95	250 (150 for caesarean section)	–

(Courtesy of Tim Smith[6])

Pharmacology

Drug	Plain Solution Concentration (%)	Plain Solution Max Dose (mg)	Plain Solution Duration (min)	Epinephrine-Containing Solution Max Dose (mg)	Epinephrine-Containing Solution Duration (min)
Short Duration					
Procaine	1-2	500	20-30	600	30-45
Chloroprocaine	1-2	800	15-30	1000	30
Moderate Duration					
Lidocaine	0.5-1	300	30-60	500	120
Mepivacaine	0.5-1	300	45-90	500	120
Prilocaine	0.5-1	350	30-90	550	120
Long Duration					
Bupivacaine	0.25-0.5	175	120-240	200	180-240
Ropivacaine	0.2-0.5	200	120-240	250	180-240

Miller's Anesthesia
2015

Pharmacology

Fiber Class	Subclass	Myelin	Diameter (μm)	Conduction Velocity (msec)	Location	Function	Susceptibility to Local Anesthetic Block
A	α	+	6-22	30-120	Efferent to muscles	Motor	++
	β	+	6-22	30-120	Afferent from skin and joints	Tactile, proprioception	++
	γ	+	3-6	15-35	Efferent to muscle spindles	Muscle tone	++++
	δ	+	1-4	5-25	Afferent sensory nerves	Pain, cold temperature, touch	+++
B		+	<3	3-15	Preganglionic sympathetic	Various autonomic functions	++
C	sC	–	0.3-1.3	0.7-1.3	Postganglionic sympathetic	Various autonomic functions	++
	dC	–	0.4-1.2	0.1-2.0	Afferent sensory nerves	Various autonomic functions Pain, warm temperature, touch	+

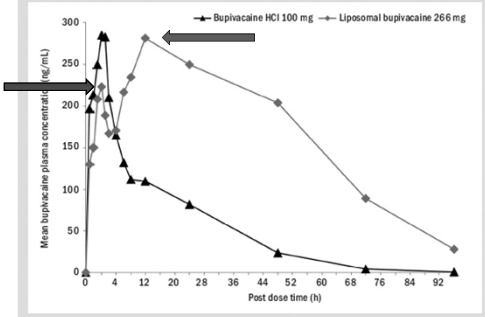
Miller's Anesthesia 2015

LA Toxicity: Plasma Concentration

- Physicochemical properties of local anesthetic agents[10]:
  - pKa (speed of onset)
    - Low pKa = more ionized form (compared to physiological pH of 7.4), so less/slower onset of block
    - Increase amount of free base to penetrate the cell membrane by increasing the pH (i.e., add bicarb) to enhance onset/block
  - Lipid Solubility or partition coefficient (potency)
    - Greater ability to penetrate the cell membrane
    - The higher the partition coefficient, the higher the lipid solubility and the greater the ability to bind and stay bound.
  - Protein Binding (duration of action)
    - LAs bind to albumin and α-1 acid glycoprotein in plasma.
    - If protein sites are saturated, plasma levels rapidly increase.
    - When plasma pH falls, LAs dissociate from proteins as well.

Figure 1

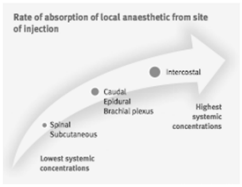
Absorption profile of liposomal bupivacaine versus bupivacaine HCl after local infiltration administration in men undergoing inguinal hernia repair



Formulary Source: Ref 28

Factors Affecting Toxicity

- Concentration of LA solution
- Total administered dose
- Vasopressors and pH modifiers
  - Epinephrine, bicarbonate, and local anesthetics themselves
- Site of injection and tissue vascularity
- pH of surrounding tissues and plasma
  - Tissue H+ decreases effect
  - Cellular H+ increases D.O.A.



(Beecroft and Davies[4])

Factors Affecting Toxicity

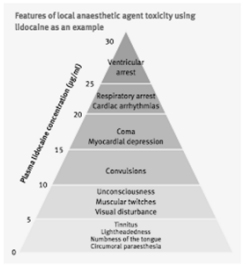
- Body Weight
  - More body fat means greater "lipid sink" and decreased toxicity.
- Age
  - In neonates, LAs compete with bilirubin for plasma protein binding sites.
  - The elderly have decreased organ function and less myelin.
- Physical status of the patient
  - Renal and hepatic dysfunction, cardiac failure, and pregnancy.
- Metabolism and clearance
  - Amides metabolized by liver, but esters broken down by plasma cholinesterase.
- Drug Interactions
  - Propanolol, cimetidine, itraconazole, and fluvoxamine.

Toxicity: Signs and Symptoms

- The "classic presentation" includes signs of CNS "excitement" followed by CNS "depression," and then signs of cardiac "excitement" and complete collapse.
- However, LAST can present as a rapidly developing seizure or CNS toxicity can be bypassed completely and complete cardiovascular collapse can be the presenting symptom.
- CNS excitement examples: metallic taste, circumoral tingling, ringing in the ears, visual disturbances or hallucinations, tremors, dizziness, and eventually convulsions.
- CNS depression examples: Apnea and coma.

Toxicity: Signs and Symptoms

- Seizure activity can often lead to signs of cardiac excitement such as hypertension, tachycardia, and ventricular tachyarrhythmias.
- Finally, cardiac depression (bradycardia, decreased contractility, pacemaker dysfunction, hypotension, and asystole) and complete cardiovascular collapse are the end result of severe LAST.



(Courtesy of Tim Smith[6])

What plan do "we" have?

- Where's your Intralipid?
- Can you rapidly access C-P bypass?
- Do you have a Dept/Practice plan?

- Corcoran W, Beck C, Gerancher JC, Butterworth J, Groban L. Anesth Analg 2006;102:S-316 (91 depts, few had a plan, thought of bypass contacts or had Intralipid)

- Corcoran et al….
- 91/135 academic anesth programs

- Those with >70 PNBs/month were 1.7x more likely to use ropivacaine, 3.9x more likely to consider lipid Rx, 3.9x more likely to have a plan for access to CPB
- Wide variability in preparedness for LAST and lack of consensus for its management

Successful use of 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest

- Rosenblatt MA, Abel M, Fischer GW, et al
- Anesthesiology 2006;105:217-8

- 58 yo male with CAD had an ISB with neurostim after 2 mg midazolam & 50 mcg fentanyl
- 20 ml 0.5% Bupivacaine & 20 ml 1.5% Mepivacaine
- 30 sec later = seizure, then hypotension, bradycardia & asystole

The treatment

- ACLS for 20 min (= A, B, C, D, E)
- Plan was to go to C-P bypass
- Given 100 ml 20% Intralipid
- One good beat, then atropine & epi, and restoration of rate, rhythm & BP
- Recovered - that's why the title is: "*Successful* use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest"

Lipid infusion resuscitation for LA toxicity

- Weinberg G. Anesth 2006;105:7-8

- Based on research after a pt with (later discovered) carnitine deficiency was toxic with 22 mg Bupivacaine during liposuction
- Talk about a bad (researcher's) day…"Doc, we can't kill the rats by asystole after the lipid infusion"
- *Then* tried intentional bupivacaine tox studies in rats, *then* in dogs, and now in man **(***a* man!)**

Weinberg has persevered

- 1 ml/kg, **now** 1.5 ml/kg bolus and 0.25 – 0.5 ml/kg/min x 30 min.
- Bolus can be repeated
- Bupiv delays the onset of myocardial acidosis so there is some inherent cardio-protection, so keep going & try lipid before quitting CPR
- Pattern per cases on www.lipidrescue.org is sz (yes/no), lo BP - brady – asystole, AND the sx recur
- Risk of the lipid dose – not known

- Lipid rescue: A step forward for patient safety? Likely so!
  - Rowlingson JC. Anesth Analg 2008;106:1133-36
  - THREE more cases of lipid rescue
  - **Questions** that remain: when to start the Rx, optimal and maximal doses, rate of administration, duration of Rx
  - Recommendations: monitor patients, use specific doses and drug, know how to contact for cardio-pulmonary bypass

- Lipid infusion therapy: Translation to clinical practice
  - Weinberg GL. Anesth Analg 2008;106:1340-42
  - The THREE cases in this issue used a **different** intralipd, used the Rx in a child, used larger doses, gave no bolus/only infusion Rx
  - View into mechanism: lipid sink and/or (+) effect of lipid on cellular oxidative metabolism
  - Don't wait for CV collapse to start the Rx

- Lipid emulsion therapy for the treatment of local anesthestic toxicity: Patient safety implications
  - Brull SJ. Anesth Analg 2008;106:1337-39
  - What are the **risks** of lipid Rx?: increased infection, thrombophlebitis, allergic reaction, emboli to the organs, pulmonary hypertension, warfarin resistance. In the short-term of Rx, what's real??
  - **ALL of these editorials recommend lipid emulsion be stocked in areas of high volume local anesthetic administration**

Treatment of LAST

- Overall, incidence of severe LAST is estimated at 7.5-20 cases per 10,000 PNBs and 4/10,000 epidurals.
- **Amer Soc Reg Anesth Guidelines**
- First, most important step, is prevention:
  - Use the lowest effective dose
  - Inject incrementally, in 3-5 ml aliquots
  - Aspirate before each injection (~2% false negative rate)
  - Use Ultrasound guidance, which may reduce the frequency of intravascular injection
  - With frequent or large doses, use an intravascular marker
    - Epinephrine for cardiac signs

Treatment of LAST

ASRA Guidelines

- Airway management is the critical first step!
  - Prevents hypoxia and acidosis
- If seizures occur, start with benzodiazepines
  - If they persist, propofol or small doses of sux may help.
- Propofol should be avoided in cardiovascular collapse!
- If cardiac arrest occurs, begin ACLS
  - Epinephrine should be used in small doses, avoid ADH!
- Begin Lipid Emulsion Therapy (Intralipid)
- Failure of ACLS and Intralipid calls for CPB, if available (know how to contact these folks)

Intralipid

- Dosing:
  - 1.5 ml/kg bolus (20%), then 0.25 ml/kg/min for 10 min.
  - Then, re-bolus and 0.5 ml/kg/min if stability not attained.
- Potential for treatment discovered by a former UVA Anesthesiology resident Guy L. Weinberg in 1998.
- Mechanism of Action: Unknown.
  - Theories:
    - Lipid Sink
    - Cardiac Myocyte FA/ATP supply.
- Risks are incredibly low: perhaps pulmonary injury & pancreatitis with very high doses.

Ultrasound guidance reduces the risk of LAST following peripheral nerve blockade

Barrington MJ, Kluger R.

RAPM 2013;38:289-99

Australian & NZ registry of 20,021 pts with 23,336 PNBs and 22 episodes of LAST

U/S DID *decrease* the incidence of LAST by >65%

MAY improve safety by less vasc puncture and/or LA dosing

LAST: Improving patient safety one step at a time

- Neal JM. RAPM 2013;38:259-61
- Slowly data are emerging that U/S reduces the rate of LAST
- Concern that practitioners will get over-confident?!
- LAST did occur in 12 of 20,000 blocks
- Therefore need to use all tools for safety, i.e. a vascular marker

Future directions in LAs

- Chemically modify a "standard" LA to dramatically increase its duration
- Encapsulate LAs other than Bupivacaine
- Find another drug (e.g. TTX) with or without encapsulation
- But, prolonged binding to Na+ channel may lead to toxicity
- Are regional LA infusions starting to look better? (Butterworth ASRA '07)

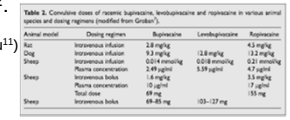
Stereoisomers & Toxicity

- Bupivacaine is a racemic mixture of stereoisomers.
- Levobupivacaine and ropivacaine are pure levo- or S(-) isomers of their respective agents.
- These three drugs are all in the same family, which also includes mepivacaine (the only short-acting of the four).
- They all share similar characteristics in terms of their physicochemical properties, except for ropivacaine having a much lower lipophilicity than the other two agents.
- For amide local anesthetics, it has been found that the "levorotatory isomer has less potential for systemic toxicity than the dextrorotatory one[11]."

Stereoisomers & CNS Toxicity

- In animal model studies, the propensity to cause seizures was found to be 1.5-2.5 times less for L-bupi and ropi, than for racemic bupivacaine[12].

(Casati and Putzu[11])



- In a study by Stewart et al, with healthy male volunteers in a double-blind, cross-over study:
  - no significant difference between L-bupi and ropi in mean time to onset of CNS symptoms with infusions of each.
- In a similar study with healthy male volunteers:
  - Doses of L-bupi and ropi were 10-25% larger than racemic bupivacaine before signs of CNS toxicity occurred[11].

- Lipid emulsion in local anesthetic toxicity

Harvey M, Cave GC. Anesth 2016;125:451-53 *preceding*: Effect of Intralipid on the dose of ropivacaine or levobupivacaine tolerated by volunteers in Anesth 2016;125;474-83 (maybe the sink theory is right-er)

The effect of lipid emulsion on pharmacokinetics of bupivacaine in rats: Long-chain triglyceride versus long-and medium-chain triglyceride (long chain more effective) Anesth Analg 2016;123:1116-1122

- An assessment of the awareness of LAST among multi-specialty postgraduate residents
- Sagir A, Goyal R. J Clin Anesth 2015;29:299-302
- 200 non-anesth residents: 70% did not aspirate before injecting, 93% didn't know the toxic dose of bupivacaine, only 70% believed that LAs could be toxic, 81% did know s/s of CV toxicity, and only 2% knew of lipid Rx

References

1) Neal JM, Bernards CM, Butterworth JF, et al. ASRA Practice Advisory on Local Anesthetic Systemic Toxicity. RAPM 2010;35:152-61

2) Neal JM, Hsiung RL, Mulroy MF, et al. ASRA Checklist improves trainee performance during a simulated episode of LAST. RAPM 2012;37(1):8-15

3) McEvoy MD, Hand WR, Stoll WD, et al. Adherence to guidelines for the management of LAST is improved by an electronic decision support tool and designated "reader". RAPM 2014;39(4):299-305

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- 4) Liu F, Wu B, Du Y, et al. Epinephrine reversed high-concentration bupivacaine-induced inhibition of Calcium channels and transient outward Potassium current channels, but not [on] Sodium channel[s] in ventricular myocytes of rats.
- BMC Anesthesiol 2015;15(66):1-12

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- Best Pract and Res Clin Anaesth 2014;28:15-27