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

- 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

<table>
<thead>
<tr>
<th>Esters</th>
<th>Amides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Procaine</td>
<td>Etidocaine</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Levobupivacaine</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Mepivacaine</td>
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<tr>
<td></td>
<td>Prilocaine</td>
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<tr>
<td></td>
<td>Ropivacaine</td>
</tr>
<tr>
<td></td>
<td>((the 2 i's Rule))</td>
</tr>
</tbody>
</table>

Pharmacology

Local Anesthetics

- Esters
  - Cocaine
  - Procaine
  - Chloroprocaine
  - Tetracaine
  - Benzocaine
- Amides
  - Bupivacaine
  - Etidocaine
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  - Lidocaine
  - Mepivacaine
  - Prilocaine
  - Ropivacaine
  - ((the 2 i's Rule))

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.

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.

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>pKa</th>
<th>Lipid Solubility</th>
<th>Protein Binding</th>
<th>Recommended Maximum Initial Dose (mg)</th>
<th>Plasma Concentration</th>
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</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>6.7</td>
<td>2.2</td>
<td>98</td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>6.1</td>
<td>1.8</td>
<td>98</td>
<td>125</td>
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</tr>
<tr>
<td>Lidocaine</td>
<td>5.4</td>
<td>1.8</td>
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<td>125</td>
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</tr>
<tr>
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<td>2.2</td>
<td>98</td>
<td>125</td>
<td>125</td>
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<tr>
<td>Levobupivacaine</td>
<td>6.6</td>
<td>2.2</td>
<td>98</td>
<td>125</td>
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Pharmacology

- LA Mechanism of Action
- LA Toxicity: Mechanism of Action
- Local Anesthetics
- Practice changes making the old tables/charts less relevant
- Ultrasound
- Adjuvant drug use – epinephrine, clonidine, opioids, dexamethasone
- More repeated injections or continuous infusions with incremental aspiration and dosing injections
- Less use of large, single doses of LAs

(Courtesy of Tim Smith)
**Pharmacology**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Solubility</th>
<th>Melting Point</th>
<th>Dissociation Velocity Constant</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20.5</td>
<td>90.5</td>
<td>Weakly ionized</td>
<td>Surface</td>
<td>Block</td>
</tr>
<tr>
<td>B</td>
<td>10.3</td>
<td>50.5</td>
<td>Weakly ionized</td>
<td>Surface</td>
<td>Block</td>
</tr>
<tr>
<td>C</td>
<td>5.0</td>
<td>30.0</td>
<td>Fully ionized</td>
<td>Surface</td>
<td>Block</td>
</tr>
</tbody>
</table>

**LA Toxicity: Plasma Concentration**

- Physicochemical properties of local anesthetic agents:
  - 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.
- Protein Binding (duration of action): binds to albumin and α1 acid glycoprotein in plasma.
- 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 vascularly
  - pH of surrounding tissues and plasma
  - Tissue H+ decreases effect
  - Cellular H+ increases D.O.A.

**Factors Affecting Toxicity**

- Body Weight: More body fat means greater “lipid sink” and decreased toxicity.
- Age: 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.

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)

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 intralipid, 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 anesthetic 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

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.

**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 one11.

**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 bupivacaine12.
  
  (Casati and Putzu11)
- 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 occurred11.
Lipid emulsion in local anesthetic toxicity
Harvey M, Cave GC. Anesth 2016;125:451-53

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

References

References

References
Tong YCI, Kaye AD, Urman RD.
Liposomal bupivacaine and clinical outcomes.
Best Pract and Res Clin Anaesth 2014;28:15-27