Managing Local Anesthetic Systemic Toxicity

NDANA Fall Educational Meeting
Kevin Buettner, PhD, CRNA
October 14th, 2016

Objectives
At the conclusion of this presentation, you will be able to:
• Discuss the pharmacodynamics and pharmacokinetics of local anesthetics as it relates to local anesthetic systemic toxicity (LAST)
• Recognize the signs and symptoms of LAST
• Discuss the treatment and management of LAST
• Identify interventions that can be utilized to decrease the incidence of LAST

A BRIEF REVIEW OF LOCAL ANESTHETICS......
Local Anesthetics

• Local anesthetics consists of:
  • Benzene ring (lipophilic)
  • Amino group (hydrophilic portion)
  • Connected by an intermediate hydrocarbon chain

• Mechanism of Action:
  • Current thought and research is focused on voltage gated sodium channel → LA causes conduction blockade.

Classification of Locals

• ESTERS
  • Procaine
  • Chloroprocaine
  • Tetracaine
  • Cocaine
  • Benzocaine

• AMIDES
  • Lidocaine
  • Etidocaine
  • Prilocaine
  • Mepivacaine
  • Bupivacaine
  • Ropivacaine

Systemic Absorption

• Degree of systemic absorption depends on:
  • Dose administered into the tissues
  • Vascularity of injection site
  • Presence of epinephrine in the solution
  • Physiochemical properties of the local

• Toxicity has a huge effect on CNS and CV systems
  • Can observe a variety of CNS and CV symptoms
    • CNS before CV
    • CV are late signs!!
CNS Toxicity

- Low plasma concentrations:
  - Produce numbness of tongue and lips due to high vascularity of these tissues
  - Also, ringing in the ears.

- As concentrations increase:
  - Local anesthetics readily cross the blood-brain barrier to cause further CNS effects.
  - Include muscle twitching, unconsciousness, seizures, coma

CV System Toxicity

- Hypotension
  - Relaxation of arteriolar vascular smooth muscle
  - Direct myocardial depression
  - Reflects decreases in SVR and CO

- At low plasma concentrations:
  - Locals effect cardiac sodium channels and contributes to the anti-arrhythmic properties of these drugs.
    - That's why we use them at therapeutic levels.

- BUT......

CV System Toxicity Cont’d

- With excessive plasma concentrations:
  - Sufficient cardiac Na+ channels become blocked so conduction and automaticity become adversely depressed.

- Specifically with excessive lidocaine:
  - Slow conduction rates manifest as prolonged P-R interval and QRS complex.
  - Gives you some warning if you have an ECG on patient.
CV System Toxicity Cont’d

• Accidental IV bupivacaine injection
  • Long-acting agent, highly tissue bound (cardiac)
  • May result in rapid hypotension, cardiac dysrhythmias and AV heart block
  • EKG changes very little before it progresses to VT and VF
  • CPR should be carried out for a prolonged period

• Threshold for Cardiotoxicity
  • May be decreased in patients taking drugs to inhibit cardiac impulse propagation like beta-blockers, digitals, and calcium channel blockers.
  • Cardiac complications are often refractory to standard treatment protocols

Manifestations of Local Anesthetic Toxicity

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Plasma Concentration (mcg/ml)</th>
<th>Order of Toxic Manifestations for any Local Anesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY</td>
<td>3 mcg/ml</td>
<td>Circumoral and tongue numbness</td>
</tr>
<tr>
<td></td>
<td>4 mcg/ml</td>
<td>Lightheadedness and tinnitus</td>
</tr>
<tr>
<td></td>
<td>6 mcg/ml</td>
<td>Visual disturbances</td>
</tr>
<tr>
<td></td>
<td>8 mcg/ml</td>
<td>Muscular twitching</td>
</tr>
<tr>
<td></td>
<td>10 mcg/ml</td>
<td>Unconsciousness</td>
</tr>
<tr>
<td></td>
<td>12 mcg/ml</td>
<td>Convulsions</td>
</tr>
<tr>
<td></td>
<td>15 mcg/ml</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>20 mcg/ml</td>
<td>Respiratory Arrest</td>
</tr>
<tr>
<td>LATE</td>
<td>26 mcg/ml</td>
<td>Cardiovascular depression → collapse</td>
</tr>
</tbody>
</table>

LAST

• Local Anesthetic Systemic Toxicity (LAST) should be considered in any patient with altered mental status, neurological symptoms, and/or cardiac instability following a regional anesthetic.

• Remember:
  • CNS Signs – may be subtle or absent
  • CV Signs – may be the only manifestation of severe LAST.
Factors that Increase Risk of LA Systemic Toxicity

- Advanced Age
- Heart Failure
- Ischemic Heart Disease
- Severe Cardiac Dysfunction (particularly very low ejection fraction)
- Conduction Abnormalities
- Metabolic Disease (e.g. mitochondrial)
- Liver Disease
- Low Plasma Protein Concentration
- Metabolic or Respiratory Acidosis
- Medications that Inhibit Sodium Channels

Prevention of LA Systemic Toxicity

- REMEMBER – Preventing is easier than treating.
- Know your maximum safe dose
- If not contraindicated, consider using a vasoconstrictor
- Always aspirate and test dose before each injection and reinjection
- Use of Ultrasound
- Fractionate dose – No more than 5ml aliquots
- Proper monitoring
- Careful selection of LA for specific purpose and attention to concentration required and dosing guidelines
- Use the least dose of LA necessary to achieve the desired extent and duration of block.
- Adequate preparation for possible resuscitation

Questions?

MOVING ON TO LIPIDS AND LAST TREATMENT.....
History

• 1884 – Cocaine used to perform nerve blocks
• 1887 – “Cocaine Toxaemia” described by Mattison
• 1905 – Procaine synthesized
• 1924 – Report from American Medical Association – 43 LA fatalities
• 1957 to 1963 – Amino amides synthesized (mepivacaine, prilocaine, bupivacaine)
• 1963 – Bupivacaine first used in clinical practice
• 1970 – Scattered reports of cardiac arrhythmias/arrests with bupivacaine
• 1977 – First report of toxicity with peripheral nerve blocks
• 1979 to 1983 – Increasing reports of toxicity causing seizures, CV collapse. Also maternal deaths associated with use of 0.75% bupivacaine in epidurals.
• 1983 – FDA: 0.75% bupivacaine no longer indicated in OB

History Cont’d

• 1998 – Dr. Guy Weinberg
  • Was doing research on carnitine deficiency
  • Noted with rats that the lethal dose of bupivacaine was increased when lipid emulsion was given and with resuscitation, it was more effective with lipid emulsion.
• 2003 – Weinberg conducted a pivotal study using 20 large dogs.
  • General anesthesia, then injected bupivacaine 10 mg/kg → cardiac arrest. 10 minutes of internal cardiac massage.
  • Randomized dogs – either received 20% lipid or saline in resuscitation
  • Group that received 20% lipid – 100% survival; Saline – 0%

Lipid Infusions

• Emulsions in Water
  • Comprised of:
    • Soybean oil
    • Egg yolk phosphatid 1%
    • Emulsifying agent
  • Particles (fat droplets): 0.5 um in diameter
  • In our blood, these fat droplets form a lipid compartment/layer from the aqueous phase.
    • “Salad dressing” in our blood

• Theory of Mechanism:
  • “Lipid sink” is created
  • Lipid bilayer sequent to oils of high lipophilicity (i.e. LA) in an expanded plasma lipid phase.
  • Bupivacaine lipid aqueous partition coefficient is almost 120
Lipid Infusion Cont’d

- 20% Lipid Emulsion – commonly used in hospitals for TPN. Typically supplied in 500 ml or 1000 ml bags.
- No need for refrigeration
- Cost

Other Applications of Lipid Infusions

- Overdoses of other lipophilic agents (i.e. calcium channel blockers, propranolol, antidepressants)

**NOTE:** Can’t use Propofol – only 1% emulsion.

- Not enough to create “sink effect” at normal doses.
- Normal or higher doses would create significant CV and hemodynamic instability.

Lipid Infusion Cont’d

- Some Risk to Consider...

Side Effects/Reactions from Lipid Emulsions:

- Contamination
- Soybean allergy
- Direct reaction
  - Pyogenic
  - Thrombophlebitis
- Pancreatitis
- Pulmonary Issues in Patients with Respiratory Issues (i.e. ARDS)

What’s the Evidence?

- Case Reports
- Studies and Trials
- Systematic Reviews
Lipid Infusion Cont’d

• What amount is too much?
  • Rat study (Hiller) in 2010
  • Gave 20% lipids at increasing doses between 20 – 80 ml/kg and then
    noted symptoms, and examined organs for damage.
  • Determined lethal dose (LD₅₀) in rats was 67.72 ± 10.69 ml/kg
  • Supports safety at current doses.

Treatment of Local Anesthetic Systemic Toxicity (LAST)

Airway Management
Seizure Suppression
Cardiopulmonary resuscitation (if needed)
Possible cardiopulmonary bypass

• Administer 20 percent lipid emulsion (values in parenthesis are for 70kg patient):
  • Bolus 1.5 mL/kg intravenously over 1 minute (~100mL)
  • Continuous infusion 0.25 mL/kg/min (~500 mL over 30 minutes)
  • Repeat bolus Q 5 minutes for persistent cardiovascular collapse.
  • Double infusion rate if blood pressure returns but remains low.
  • Continue infusion for a minimum of 30 minutes.

• NOTE: Obviously.....the case gets cancelled!! (maybe???)

Source: ASRA (2011)
Timing of Lipid Infusion

- Controversial
- Not too early... but not too late.

Current Recommendation: Implement based on clinical severity and rate of progression of LAST.

LAST Treatment Cont’d

**NOTES:**
- For seizure suppression – benzodiazepines are preferred
- Epinephrine
  - Can impair resuscitation from LAST and reduce efficacy of lipid rescue.
  - Avoid high doses of epinephrine. Use smaller doses (e.g. 1 mcg/kg) for treating hypotension.
- May require prolonged resuscitation effort
- Cardiopulmonary bypass may be necessary. If it is unavailable where you are, consider transfer to facility with that capability.

LAST Treatment Cont’d

**NOTES Cont’d:**

**AVOID:**
- Vasopressin, calcium channel blockers, beta blockers, or local anesthetic
- Propofol in patients having signs of cardiovascular instability
- Prolonged monitoring (> 12 hours) recommended after any signs of cardiac toxicity because CV depression due to LAs can persist or recur after treatment.

- Report case on [www.lipidrescue.org](http://www.lipidrescue.org)
Some Ideas.....

• Develop a Lipid Rescue kit. Put kit in proximity where regional and neuraxial anesthesia are being performed.

• Annual Staff Education – interdisciplinary

• Annual Mock LAST Codes

Lipid Rescue Kits

• Consider placing in any area where local anesthetics are being used.

• Contents:
  • 500-1000ml bag of 20% lipid emulsion
  • IV Tubing (macrodrip 10-15 gtts/ml)
  • 2 – 50ml Syringes
  • 2 – Needles
  • Copy of checklist
LAST Kit Cont’d
Include in Kit:

Conclusion

• **REMEMBER** – Preventing is easier than treating.
• Know your maximum safe dose
• If not contraindicated, consider using a vasoconstrictor
• Always aspirate and test dose before each injection and reinjection
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References and Resources

• American Society of Regional Anesthesia and Pain Medicine. Website: https://www.asra.com
• Drasner, K. (2010). Local anesthetic systemic toxicity: A historical perspective. Regional Anesthesia and Pain Medicine, 35(2), 162-166. doi: 10.1097/AAP.0b013e3181d2306c
• The New York School of Regional Anesthesia (NYSORA). Website: http://www.nysora.com
THE END

Any questions, comments, or discussion??