Local Anaesthetic Systemic Toxicity (LAST)

Part II Course, June 2012

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St Vincent’s Hospital, Melbourne
LAST quickly became noted as a serious complication after introduction of cocaine into clinical practice.

Two critical determinants of cocaine toxicity were noted: site of injection and drug dosage (1890).

The need to fractionate the injection and limit the dosage and concentration of cocaine. Important predisposing factors were sites of injection and patient co-morbidities (1924).
History

- “the lack of preparedness of operators to deal with such incidents and that an important responsibility of physicians was to report such complications.” (1924)

- introduction of two long-acting lipid soluble local anesthetics, bupivacaine and etidocaine in the 1960’s and 1970s
History

- 23 cases of fetal bradycardia and death from 19,907 obstetric patients who received 20 mL of 0.5% bupivacaine for paracervical block were reported in a survey conducted in Germany.
- 1960s-1970s complications were mostly thought to be CNS.
- CV features were initially thought to be from other sources, e.g. epidural.
History

- 23 cases of fetal bradycardia and death from 19,907 obstetric patients who received 20 mL of 0.5% bupivacaine for paracervical block were reported in a survey conducted in Germany.

- 1960s-1970s complications were mostly thought to be CNS.

- CV features were initially thought to be from other sources, e.g. epidural, patient co-morbidities, or hypoxia, acidosis.
Direct cardiac toxicity of bupivacaine was considered

Prentiss JE: Cardiac arrest following caudal anesthesia. Anesthesiology 1979; 50: 51-3

Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979; 51: 285-7

In case reports reviewed, seizures and cardiovascular collapse occurred almost simultaneously
Several experimental studies have demonstrated that etidocaine and bupivacaine have a much lower margin between CNS and CV toxicity compared to lignocaine.

Airway maintenance and oxygenation are the first priority in treatment of LAST.
In 1983, the manufacturers of bupivacaine modified their product information, advising against the use of 0.75% bupivacaine, the use of any concentration of bupivacaine for paracervical block or intravenous regional anesthesia and stressed the importance of a test dose and incremental injections.
Improved safety

✓ widespread adoption of test doses
✓ incremental dosing
✓ improved monitoring
✓ improved vigilance and education
✓ use of the lowest possible volume and concentration of local anesthetic to achieve effective anesthesia/analgesia.

# Epidemiology

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence n per 10,000, 95% CI</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore</td>
<td>1.4 (0.8 - 2.2)</td>
<td>epidural, caudal, PNB, seizures, no CV collapse</td>
</tr>
<tr>
<td>Brown D.L., <em>Anesth Analg.</em> 1995</td>
<td>1.0 (0.7 - 1.4)</td>
<td>epidural, caudal, brachial plexus, seizures</td>
</tr>
<tr>
<td>Auroy Y., <em>Anesthesiology.</em> 1997</td>
<td>0.4 (0.2 -0.5)</td>
<td>epidural, PNB, IV regional, seizures</td>
</tr>
<tr>
<td>Auroy Y., <em>Anesthesiology.</em> 2002</td>
<td>0.1 (0.04 - 0.3)</td>
<td>PNB, seizures</td>
</tr>
<tr>
<td>Barrington M.J. <em>Reg Anesth Pain Med.</em> 2009</td>
<td>0.98 (0.42 -1.9)</td>
<td>PNB, minor LAST, seizures</td>
</tr>
</tbody>
</table>
Presentation

- Minor: 59%
- Major: 36%
- Cardiac arrest: 5%

22 cases, 2007-2012
Denominator 25,338

from Australian and New Zealand Registry of Regional Anaesthesia

Monday, 25 June 12
Prevention

“There is no single measure that can prevent LAST in clinical practice”

Prevention - Dose Limitation

Use the lowest effective dose of local anaesthetic
Prevention - Dose Limitation

Use the lowest effective dose of local anaesthetic

<table>
<thead>
<tr>
<th>Procedure number</th>
<th>Dose (mg/kg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 5000</td>
<td>1.88</td>
</tr>
<tr>
<td>5001 - 10,000</td>
<td>1.67</td>
</tr>
<tr>
<td>10,001 - 15,000</td>
<td>1.42</td>
</tr>
<tr>
<td>15,001 - 20,000</td>
<td>1.32</td>
</tr>
<tr>
<td>20,001 - 25,000</td>
<td>1.36</td>
</tr>
</tbody>
</table>

*ropivacaine, from Australian and New Zealand Registry of Regional Anaesthesia
Prevention - Incremental Injection

- e.g. 3-5 mL aliquots, wait 15-30 sec between each injection
- Ideally wait one circulation time
Prevention - Local Anesthetics with Lower Toxicity

<table>
<thead>
<tr>
<th>LA type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropivacaine</td>
<td>77.5</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>6.7</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3.8</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>1.7</td>
</tr>
<tr>
<td>Ropiv/Ligno</td>
<td>9.0</td>
</tr>
</tbody>
</table>

from Australian and New Zealand Registry of Regional Anaesthesia, n = 25, 000
Prevention - Aspiration of Needle or Catheter

- Aspiration of Needle or Catheter before each injection
- 2% false-negative rate
Prevention - Marker of Intravascular Injection

- Ideal test dose
- Adrenaline 15 mcg
- Fentanyl in obstetrics
- Limitations
Prevention - Imaging

- Potential mechanisms why Ultrasound may reduce incidence of LAST:
Ultrasound-guidance

- Potential mechanisms why US may reduce incidence of LAST:
  - Reduced local anaesthetic requirements
  - Direct observation of intravascular injection
  - Lack of injectate spread around target
  - Incremental approach of US-guided technique
from Australian and New Zealand Registry of Regional Anaesthesia, 22 cases, 2007-2012, denominator 25,338
### Ultrasound imaging as a covariate

<table>
<thead>
<tr>
<th></th>
<th>No Ultrasound</th>
<th>Ultrasound</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No LAST events</strong></td>
<td>4736</td>
<td>20,390</td>
<td>25,126</td>
</tr>
<tr>
<td><strong>LAST events</strong></td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4,747</td>
<td>20,401</td>
<td>25,148</td>
</tr>
</tbody>
</table>

P = 0.001 Fisher’s Exact Test, No US compared with US
### Block category as a covariate

<table>
<thead>
<tr>
<th>Block category</th>
<th>Upper</th>
<th>Paravertebral</th>
<th>Trunk</th>
<th>Lower</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LAST events</td>
<td>7,422</td>
<td>1,651</td>
<td>3,914</td>
<td>12,314</td>
<td>25,301</td>
</tr>
<tr>
<td>LAST events</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>7,434</td>
<td>1,657</td>
<td>3,914</td>
<td>12,318</td>
<td>25,323</td>
</tr>
</tbody>
</table>

*P < 0.0005 Fisher’s Exact Test*
from Australian and New Zealand Registry of Regional Anaesthesia, *n/1000 95% CI

Upper Limb: 1.61* (0.8 - 2.8) n = 12
Paravertebral: 3.62* (1.3 - 7.9) n = 6
Trunk: 0* (0.09 - 0.83) n = 0
Lower Limb: 0.32* (0.09 - 0.83) n = 4
<table>
<thead>
<tr>
<th></th>
<th>Block category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper</td>
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<tr>
<td>No LAST events</td>
<td>7,422</td>
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<tr>
<td>n/1000 95% CI</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>(0.8 - 2.8)</td>
</tr>
</tbody>
</table>

\[ P < 0.0005 \text{ Fisher’s Exact Test} \]
Logistic regression model: covariates entered if $P<0.2$

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>$P$-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage*</td>
<td>1.58</td>
<td>$&lt; 0.0005$</td>
<td>1.36 - 1.83</td>
</tr>
<tr>
<td>Upper Limb</td>
<td>3.96</td>
<td>0.03</td>
<td>1.16 - 13.5</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>7.04</td>
<td>0.003</td>
<td>1.96 - 25.3</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>0.20</td>
<td>0.001</td>
<td>0.08 - 0.50</td>
</tr>
</tbody>
</table>

*Odds ratio applies to each 1mg/kg increase
Prevention

“There is no single measure that can prevent LAST in clinical practice”

Prevention

Choice of local anaesthetic
Dose limitation
Dose fractionation
Aspiration of needles and catheters
Marker of intravascular injection
Imaging
Management
APPENDIX 3

AMERICAN SOCIETY OF
REGIONAL ANESTHESIA AND PAIN MEDICINE

Practice Advisory on Treatment of Local Anesthetic Systemic Toxicity

For Patients Experiencing Signs or Symptoms of Local Anesthetic Systemic Toxicity (LAST)

• Get Help
• Initial Focus
  o Airway management: ventilate with 100% oxygen
  o Seizure suppression: benzodiazepines are preferred
  o Basic and Advanced Cardiac Life Support (BLS/ACLS) may require prolonged effort
• Infuse 20% Lipid Emulsion (values in parenthesis are for a 70 kg patient)
  o Bolus 1.5 mL/kg (lean body mass) intravenously over 1 min (~100 mL)
  o Continuous infusion at 0.25 mL/kg/min (~18 mL/min; adjust by roller clamp)
  o Repeat bolus once or twice for persistent cardiovascular collapse
  o Double the infusion rate to 0.5 mL/kg per minute if blood pressure remains low
  o Continue infusion for at least 10 mins after attaining circulatory stability
  o Recommended upper limit: approximately 10 mL/kg lipid emulsion over the first 30 mins
• Avoid vasopressin, calcium channel blockers, β-blockers, or local anesthetic
• Alert the nearest facility having cardiopulmonary bypass capability
• Avoid propofol in patients having signs of cardiovascular instability
• Post LAST events at www.lipidrescue.org and report use of lipid to www.lipidregistry.org
AAGBI Safety Guideline
Management of Severe Local Anaesthetic Toxicity

1 Recognition

Signs of severe toxicity:
- Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
- Local anaesthetic (LA) toxicity may occur sometime after an initial injection

2 Immediate management

- Stop injecting the LA
- Call for help
- Maintain the airway and, if necessary, secure it with a tracheal tube
- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Assess cardiovascular status throughout
- Consider drawing blood for analysis, but do not delay definitive treatment to do this

3 Treatment

IN CIRCULATORY ARREST
- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory to treatment
- Consider the use of cardiopulmonary bypass if available

GIVE INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)
- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1 h
- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

WITHOUT CIRCULATORY ARREST
Use conventional therapies to treat:
- Hypotension,
- Bradycardia,
- Tachyarrhythmia

CONSIDER INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)
- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

4 Follow-up

- Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved
- Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days
- Report cases as follows:
  - in the United Kingdom to the National Patient Safety Agency (via www.npsa.nhs.uk)
  - in the Republic of Ireland to the Irish Medicines Board (via www.imb.ie)
- If lipid has been given, please also report its use to the international registry at www.lipidregistry.org. Details may also be posted at www.lipidrescue.org

Your nearest bag of Lipid Emulsion is kept

This guideline is not a standard of medical care. The ultimate judgement with regard to a particular clinical procedure or treatment plan must be made by the clinician in the light of the clinical data presented and the diagnostic and treatment options available.

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