Local Anaesthetic Systemic Toxicity

By the perioperativeCPD team

Introduction

Local anaesthetic systemic toxicity (LAST) has been a known complication of local anaesthetics since the first use of cocaine as a topical anaesthetic in the late 1800’s, although modern local anaesthetics such as lidocaine and bupivacaine are safer and less likely to cause LAST. Recently released levobupivacaine and ropivacaine increase safety margins even further but local anaesthetic toxicity although rare, still occurs and its consequences can be devastating.

In 2004 Mayra Cabrera, a theatre nurse died from LAST shortly after delivery of her baby boy when her epidural infusion of bupivacaine was mistakenly connected to her i.v. line.
**How does it occur?**
Systemic toxicity of local anaesthetics can occur because of the administration of an excessive dose, with rapid absorption, or because of an accidental intravenous injection. This is because local anaesthetics work by blocking sodium (Na\(^+\)) channels preventing the conduction of nerve impulses to the brain. These sodium channels are not exclusive to nerves and can affect the cardiac and central nervous system in high concentrations.

Systemic toxicity is typically manifested firstly as central nervous system (CNS) and then cardiovascular toxicity. This is because the CNS is more susceptible to the effects of LAST than the cardiovascular system.

However, bupivacaine toxicity may not adhere to this sequence, and cardiac toxicity may precede the CNS symptoms. As result, bupivacaine toxicity may be sudden and catastrophic.

**Which sites have the highest risk of local anaesthetic toxicity?**
Irrelevant of the local anaesthetic used, systemic absorption, and therefore the risk of toxicity increases in the following order:

- **Lowest**
  - Subcutaneous injection
  - Sciatic and femoral block
  - Brachial plexus block
  - Epidural
  - Caudal
  - Intercostal block

- **Highest**
  - Inadvertent intravenous injection
What are the signs and symptoms of Systemic Local Anaesthetic Toxicity?

Central nervous system
The presenting features of local anaesthetic toxicity vary widely and may occur up to an hour after administration. The first signs are usually CNS excitation. These can include:

- tongue and circumoral (around the mouth and lips) numbness
- light-headedness and dizziness
- difficulty focusing
- tinnitus
- confusion

Followed by:

- Agitation
- Shivering
- myoclonia (jerks of the eyelids)
- tremors
- muscle twitching. Muscle twitching often precedes seizures.

As the systemic local anaesthetic level rises CNS excitation is followed by CNS depression and convulsions occur. The seizure activity ceases rapidly and ultimately is replaced by respiratory depression and respiratory arrest. Urgent intubation and ventilation may be required. In the presence of other CNS depressant drugs (e.g., premedication such as midazolam), CNS depression can develop without the preceding excitatory phase.

Cardiovascular
All local anaesthetics can induce cardiac arrhythmias, and all, except cocaine, are myocardium depressants.

The sequence of cardiovascular events is ordinarily as follows;

1) Low blood levels of local anaesthetic usually generate a small increase in cardiac output, blood pressure, and heart rate, which is most likely due to a boost in sympathetic activity and direct vasoconstriction.
2) As the blood level of local anaesthetic rises, hypotension occurs as a result of peripheral vasodilation which is due to relaxation of the vascular smooth muscles and myocardial depression.
3) Any further rise of local anaesthetic blood levels leads to severe hypotension, resulting from the combination of reduced peripheral vascular resistance, reduced cardiac output, sinus bradycardia and/or malignant arrhythmias. Eventually, extreme hemodynamic instability will lead to cardiac arrest.
Bupivacaine is different in the fact that it is more cardiotoxic than other local anaesthetics. The cardiovascular effects and collapse may occur before the CNS effects. Cardiac resuscitation is also more difficult after a bupivacaine induced cardiac arrest as it binds more firmly to the receptors on the heart and it takes longer to clear, needed prolonged resuscitation. Levobupivacaine and ropivacaine are newer versions of bupivacaine and the manufacturers claim they are less toxic.

Acid-base status also plays an important role in local anaesthetic toxicity. Hypercarbia lowers the seizure threshold and enhances cerebral blood flow; consequently, more local anaesthetic is made accessible to the cerebral circulation. Hypercarbia and/or acidosis also reduce the binding of local anaesthetics by plasma proteins, and as a result, the fraction of free drug readily available for diffusion expands.

Signs of local anaesthetic toxicity typically appear 1 to 5 minutes after injection, but onset may vary from 30 seconds to as long as 60 minutes.

**Prevention**

Prevention of LAST is the key to safer practice. The selection of the type, dose, and concentration of the local anaesthetic, and the regional anaesthesia technique, are important. Epidurals, which are of particularly high risk of intravascular placement, should have a test dose to confirm their placement. As a rule, the optimal dose and concentration is the lowest one that achieves the aimed for effect.

It is important to use slow, incremental injections of local anaesthetic with frequent aspiration to ensure the drug is not delivered i.v. or intra-arterial. If possible, ask the patient about any symptoms. It is prudent to decrease the local anaesthetic dosage in elderly or debilitated patients and in any patient with diminished cardiac output. However, there are no firm recommendations on the degree of dose reduction. Pregnant patients are also at a higher risk of toxicity. Doses will also need to be reduced in patients with liver or kidney damage because of impaired metabolism and excretion.

The effects of pre-treatment of local anaesthetic patients with a benzodiazepine are often debated and while benzodiazepines lower the probability of seizures they can also mask the early signs of toxicity.
What is the safe limit for local anaesthetics?
The table below shows the recommended maximum doses of common local anaesthetics. Any doses of local anaesthetic drugs, administered into different areas of the body, contribute to an overall maximum dose for a particular patient. If the maximum recommended dose of one local anaesthetic has been reached no further local anaesthetic should be given.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plain</th>
<th>With adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>3mg/kg</td>
<td>7mg/kg</td>
</tr>
<tr>
<td>Bupivacaine (Chiocaine)</td>
<td>2mg/kg</td>
<td>2mg/kg (no change with adrenaline)</td>
</tr>
<tr>
<td>Ropivacaine (Noropin)</td>
<td>3mg/kg</td>
<td>3mg/kg (no change with adrenaline)</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>2mg/kg</td>
<td></td>
</tr>
<tr>
<td>Prilocaine</td>
<td>6mg/kg</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>3mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

Working out concentrations:

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Strength mg/ml</th>
<th>Example: 1% lidocaine (no adrenaline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25%</td>
<td>2.5mg/ml</td>
<td>In a 70kg patient the maximum dose is 210mg (70kg x 3mg)</td>
</tr>
<tr>
<td>0.50%</td>
<td>5.0mg/ml</td>
<td>So 210mg of 1% lidocaine divided by 10 mg/ml = 21mls. (210mg / 10mg/ml = 21 ml)</td>
</tr>
<tr>
<td>1.0 %</td>
<td>10.0mg/ml</td>
<td></td>
</tr>
</tbody>
</table>

Note: Many anaesthetists when using combined nebulisation and topical anaesthesia for fibre-optic intubation use up to 9 mg/kg of lidocaine. This is because a high percentage of it not absorbed and is effectively wasted.

Why does adrenaline increase the dose?
It is peak blood levels of a local anaesthetic that cause toxicity so when adrenaline is added to some local anaesthetics (principally lidocaine) it causes vasoconstriction around the injection site, therefore slowing the systemic uptake and reducing peak blood levels. This allows higher doses to be used.

Adrenaline in a 1 in 200,000 concentration added to a local anaesthetic solution also serves as a test of intravascular injection. The adrenaline will produce tachycardia, hypertension and T wave changes when injected intravascularly.
Management
Early recognition of toxicity and immediately stopping the administration of the local anaesthetic are of crucial importance. Treatment should be supportive, treating convulsions and managing cardiac arrhythmias with established guidelines. Help should be called for, i.v. access confirmed or obtained, monitoring connected, the airway maintained and 100% oxygen used. Intubate and ventilate if needed. Neurological parameters and cardiovascular status should be assessed until the patient is completely asymptomatic and stable.

In the U.K. there should be local anaesthetic toxicity boxes available with 2 bags of Intralipid 20% and a copy of the AAGBI treatment guidelines. (See appendix one)

Administration of a benzodiazepine, thiopental or propofol to control seizures is indicated. Early treatment of convulsions is particularly meaningful because convulsions can result in metabolic acidosis, thus aggravating the situation. Propofol is often the most available drug but should not be the first choice as it is a cardiac depressant.

Suggested doses:
- Midazolam 3-10mg
- Diazepam 5-15mg
- Propofol 20-60mg
- Thiopental 50-150mg

Malignant arrhythmias and asystole are managed using ALS resuscitation protocols. Recovery from local anaesthetic-induced cardiac arrest ranges from several minutes to prolonged resuscitation of over an hour with bupivacaine-induced LAST. In this later case a mechanical chest compression device (i.e. thumper) may prove to be invaluable. The rationale of this approach is to maintain the circulation until the local anaesthetic is redistributed or metabolised below the level associated with cardiovascular toxicity, at which time spontaneous circulation should resume. If rapid access to cardiopulmonary bypass is available, this should be considered.

There is debate over which vasopressors and what doses are best during LAST although ephedrine, phenylephrine, noradrenaline and adrenaline all indicated. If there is uncertainty then adhering to the ALS algorithms is the safest course of action.

Amiodarone, as in the ALS algorithm, can be used to treat ventricular arrhythmias. DO NOT GIVE LIDOCAINE as an anti-arrhythmic.

Lipid infusion
Administration of the lipid emulsion has become an important addition to the treatment of severe local anaesthetic toxicity. Based on recent studies and case reports, starting an infusion of lipid emulsion (Intralipid 20%), especially in those cases where symptoms of cardiac toxicity are present, should be a priority. There is a mounting consensus that infusion of Intralipid may be initiated early, to prevent, rather than treat cardiac arrest.

The mechanism of action of a lipid infusion is not clear but it one theory is that may act as a lipid sink helping redistribute the local anaesthetic away from target organs i.e. the heart. This is especially relevant where bupivacaine toxicity in involved due to its long half-life and affinity for the heart.
Propofol is not an adequate alternative for treatment with Intralipid, as the doses required would be too high and would cause further cardiovascular depression. It can be used to control seizures where small divided doses are appropriate.

Intralipid 20% is given as simultaneous boluses and infusion based on weight. After 5 minutes a second bolus can be given and the infusion rate doubled if cardiovascular stability has not returned. A 3rd and final bolus can be given after a further 5 minutes if the total maximum dose has not been reached.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Initial bolus (1.5ml/kg) over 1 min</th>
<th>Infusion mls/hr (15ml/kg/hr)</th>
<th>Double infusion rate (30ml/kg/hr)</th>
<th>Maximum total dose (12ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>60</td>
<td>600</td>
<td>1200</td>
<td>480</td>
</tr>
<tr>
<td>50</td>
<td>75</td>
<td>750</td>
<td>1500</td>
<td>600</td>
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<tr>
<td>60</td>
<td>90</td>
<td>900</td>
<td>1800</td>
<td>720</td>
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<td>105</td>
<td>1050</td>
<td>2100</td>
<td>840</td>
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<td>1200</td>
<td>2400</td>
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<tr>
<td>90</td>
<td>135</td>
<td>1350</td>
<td>2700</td>
<td>1080</td>
</tr>
<tr>
<td>100</td>
<td>150</td>
<td>1500</td>
<td>3000</td>
<td>1200</td>
</tr>
</tbody>
</table>

Continue infusion until cardiovascular stability returns or maximum dose of Intralipid is given. Note: the total maximum dose can be reached in less than 20 minutes.

Following the return of spontaneous circulation the patient should be transferred to the appropriate ICU/high dependency unit as per local protocols.

**Prilocaine**

Although LAST from prilocaine is uncommon because it is metabolised rapidly, high doses (>600mg in an adult) may cause methaemogloinaemia (a blood disorder in which an abnormal amount of methaemoglobin is produced). This can be treated with methylene blue.

**Conclusion**

Local anaesthetic systemic toxicity is rare but when it does occur its onset may be sudden and life-threatening so it is prudent to spend time preventing rather than treating it. All theatre staff should be aware of the doses limits of local anaesthetics they use as well as the causes, signs and treatment of LAST. This also includes knowing where the LAST box and intralipid are kept. Remember, when it does occur, get help fast.
References


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Appendix one: AAGBI Guideline- Management of severe local anaesthetic toxicity

## 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 some time 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

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Your nearest bag of Lipid Emulsion is kept

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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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An approximate dose regimen for a 70-kg patient would be as follows:

**IMMEDIATELY**

- Give an initial intravenous bolus injection of 20% lipid emulsion 100 ml over 1 min  
  AND  
- Start an intravenous infusion of 20% lipid emulsion at 1000 ml.h⁻¹

**AFTER 5 MIN**

- Give a maximum of two repeat boluses of 100 ml  
  AND  
- Continue infusion at same rate but double rate to 2000 ml.h⁻¹ if indicated at any time

**Do not exceed a maximum cumulative dose of 840 ml**

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This AAGBI Safety Guideline was produced by a Working Party that comprised: Grant Cave, Will Harrop-Griffiths (Chair), Martyn Harvey, Tim Meek, John Picard, Tim Short and Guy Weinberg. This Safety Guideline is endorsed by the Australian and New Zealand College of Anaesthetists (ANZCA).

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