Local anaesthetic systemic toxicity (LAST)

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Incidence

Peripheral Nerve Blocks:

7.5 per 10 000 in 1997
2.5 per 10 000 in 2004
9.8 per 10 000 in 2009
8.7 per 10 000 in 2013 USS guided

Epidural anaesthesia:

1.2–11 per 10 000 in 1993-1997

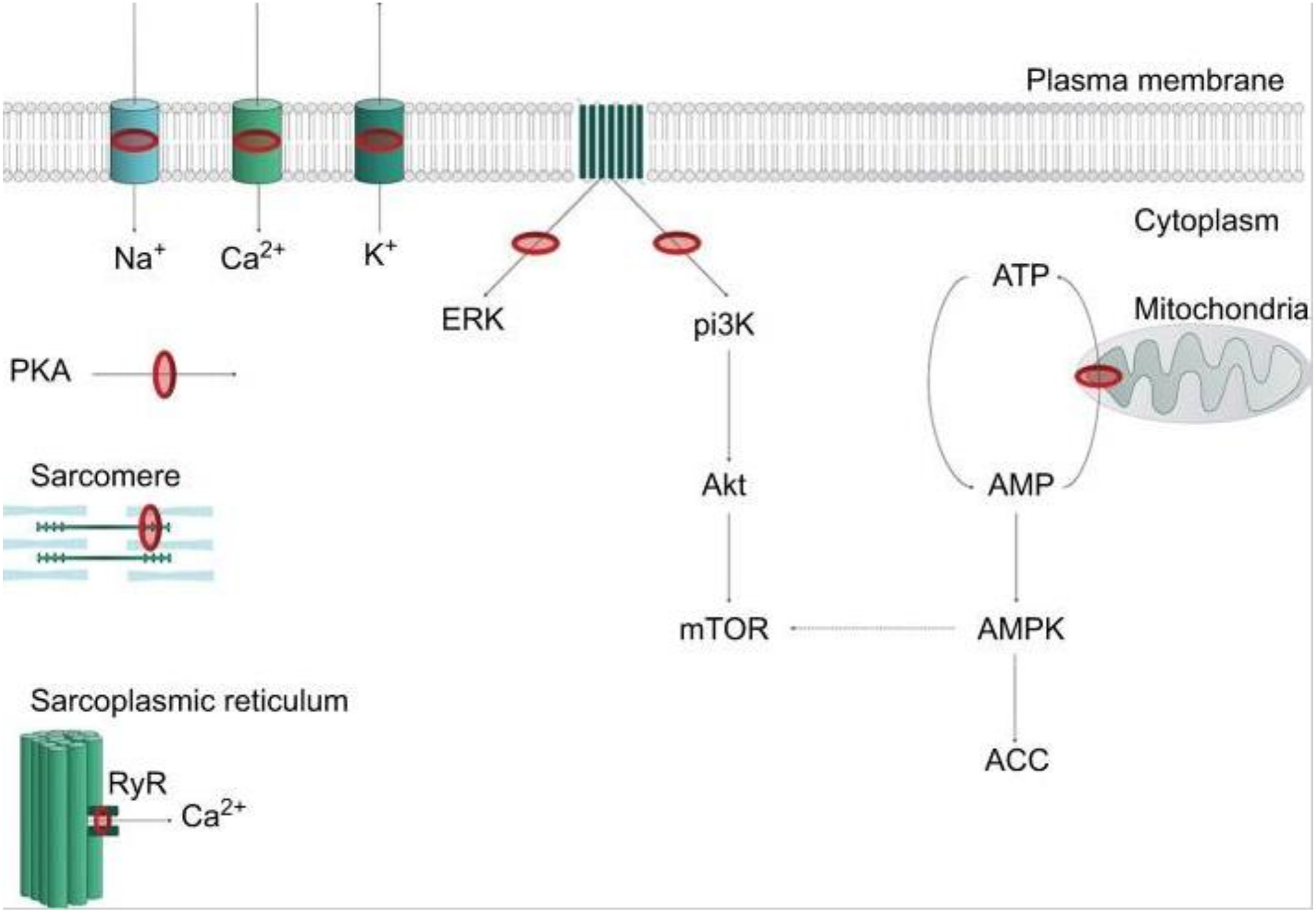
Mechanism of action

LA attach to Na channel, thereby inhibiting neuronal ion transfer and depolarisation, and preventing neuronal transmission.

LA bind to and block K+ channels, Ca2+ channels, the Na+–K+ ATPase channel.

LA interfere with intracellular and transmembrane cell signalling, affecting the metabolic processes of cyclic adenosine monophosphate, protein kinase B (Akt), and 5-adeonosine monophosphate activated protein kinase (AMPK).

LAs have also been shown to impair mitochondrial metabolism, adenosine triphosphate production, inhibit the ryanodine receptor at the sarcoplasmic reticulum, and reduce Ca2+ sensitivity of myofilaments.



Representation of key LA cellular targets contributing to local anesthetic systemic toxicity.
Notes: In the plasma membrane, LAs block the Nav channel (Na^+), potassium (K^+) and calcium channels (Ca^{2+}). Inhibition of second messenger systems on metabotropic transmembrane G-protein-coupled receptors leads to inhibition of ERK and pi3K. This leads to dysregulation of downstream kinase pathways, including a reduction in Akt and, thus, mTOR. Mitochondrial phosphorylation of AMP to ATP is inhibited, leading to an increase in the inhibitory, energy-sensing kinase AMPK, which in turn further mitigates mTOR. Other inhibitory targets include PKA, calcium-dependent contractility inhibition at the sarcomere, and modulation of the RyR. Red rings represent sites of action of LAs. Dotted lines represent inhibitory actions.
Abbreviations: AMP, adenosine monophosphate; ATP, adenosine triphosphate; LA, local anesthetic; RyR, ryanodine receptor.

Mechanism of toxicity

LA reaches the circulation via systemic absorption or accidental intravascular injection.

Lipophilic LA rapidly cross cell membranes

In the brain - affect the balance between inhibitory and excitatory pathways. Initially compromises cortical inhibitory pathways by blockade of Na channels, disrupting inhibitory neurone depolarisation

In the heart - effects on sodium, potassium, and calcium channels block conduction - dysrhythmia and reduce contractility.
Sodium channel blockade course more negative resting membrane potential - leading to prolonged PR, QRS, and ST intervals

LA disrupt intracellular signals at metabotropic receptors, leading to reduced cyclic adenosine monophosphate concentrations - reduced contractility.

Risk factors

Type of LA

- Duration of action

- Formulation

- Intrinsic vasoactive effect:
  Levobupivacaine/ ropivacaine - vasoconstrictor Bupivacaine - vasodilator

- CC/CNS ratio - ratio of the dose required to produce cardiovascular collapse to that required to induce seizures:
  Bupivacaine ratio 2.0 / Lidocaine ratio 7.1

Risk factors

Dose LA

	Max. dose without epinephrine (mg kg^{-1})	Max. dose with epinephrine (mg kg^{-1})
Lidocaine	3	7
Bupivacaine	2	2
Ropivacaine	3	3
Prilocaine	6	—

Block related

- site of block

- single vs continuous

- conduct of block

Risk factors

Patient factors

- Organ dysfunction:
cardiac disease - decompensated heart failure, severe valvular pathology, depressed ventricular function
hepatic or renal dysfunction - decreased metabolism and clearance
higher level of circulating drug

serum level of the binding proteins - malnutrition, liver/renal failure - decreased albumin

- Extremes of age:
diminished muscle mass - higher dose of drug for their weight
elderly are more likely to have organ dysfunction
children - early symptoms will be missed, CNS/cardiac first sign of toxicity as anaesthetised

- Pregnancy - accelerated perfusion of injection sites, rapid LA absorption, and higher peak free LA concentrations

Presentation

Central nervous system toxicity

Two-stage process - initial excitatory
- depressive phase.

Features:
- peri-oral tingling
- tinnitus
- slurred speech
- lightheadedness
- tremor
- change in mental status (confusion or agitation)
- generalised convulsions
- coma
- respiratory depression

Presentation

Cardiovascular system toxicity

Three phases:

- initial phase - hypertension and tachycardia
- intermediate phase - myocardial depression and hypotension
- terminal phase - peripheral vasodilatation, severe hypotension, arrhythmias (sinus bradycardia, conduction blocks, ventricular tachyarrhythmias, and asystole)

Cardiovascular collapse may occur without preceding neurological changes

Presentation could be delayed

Prevention

Ultrasound guidance:
- direct visualisation of LA spread
- detection of intravascular injection
- smaller volumes of LAs

Intravascular markers:
- 10–15 µg of adrenaline with test dose
- increase in heart rate of >= 10/min, systolic blood pressure >= 15 mm Hg

Incremental injection with aspiration:
- 3-5 ml plus test dose

Less toxic drugs

Lowest effective dose:
- reduce dose for susceptible to LAST patients

Use of NRFit yellow syringes

Clear labelling and communication

Treatment

1. Stop injecting the local anaesthetic (remember infusion pumps).
2. Call for help and inform immediate clinical team of problem.
3. Call for cardiac arrest trolley and lipid rescue pack.
4. Give 100% oxygen and ensure adequate lung ventilation:
    - Maintain the airway and if necessary secure it with a tracheal tube.
    - Hyperventilation may help reduce acidosis.
5. Confirm or establish intravenous access.
6. **If circulatory arrest:**
    - Start continuous CPR using standard protocols.
    - **Give** intravenous lipid emulsion (Box A).
    - Recovery may take >1 hour.
    - Consider the use of cardiopulmonary bypass if available.

   If no circulatory arrest:
    - Conventional therapies to treat hypotension, brady- and tachyarrhythmia.
    - **Consider** intravenous lipid emulsion (Box A).
7. Control seizures with small incremental dose of benzodiazepine, thiopental or propofol.

Treatment

Box A: LIPID EMULSION REGIME

USE 20% Intralipid® (propofol is not a suitable substitute)

Immediately

- ☐ Give an initial i.v. bolus of lipid emulsion 1.5 $ml.kg^{-1}$ over 1 min (~100 ml for a 70 kg adult)
- ☐ Start an i.v. infusion of lipid emulsion at 15 $ml.kg^{-1}.h^{-1}$ (17.5 $ml.min^{-1}$ for a 70 kg adult)

At 5 and 10 minutes:

- ☐ Give a repeat bolus (same dose) if:
  - o cardiovascular stability has not been restored or
  - o an adequate circulation deteriorates

At any time after 5 minutes:

- ☐ Double the rate to 30 $ml.kg^{-1}.h^{-1}$ if:
  - o cardiovascular stability has not been restored or
  - o an adequate circulation deteriorates

Do not exceed maximum cumulative dose 12 $ml.kg^{-1}$ (70 kg: 840 ml)

The scavenging effect is moderated by the lipid emulsion's ability to take up lipophilic moieties and transfer them around the blood to sites of storage and detoxification. This provides a "lipid shuttle" effect.

3-10 Local anaesthetic toxicity v.1

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 toxicity may occur some time after an initial injection.

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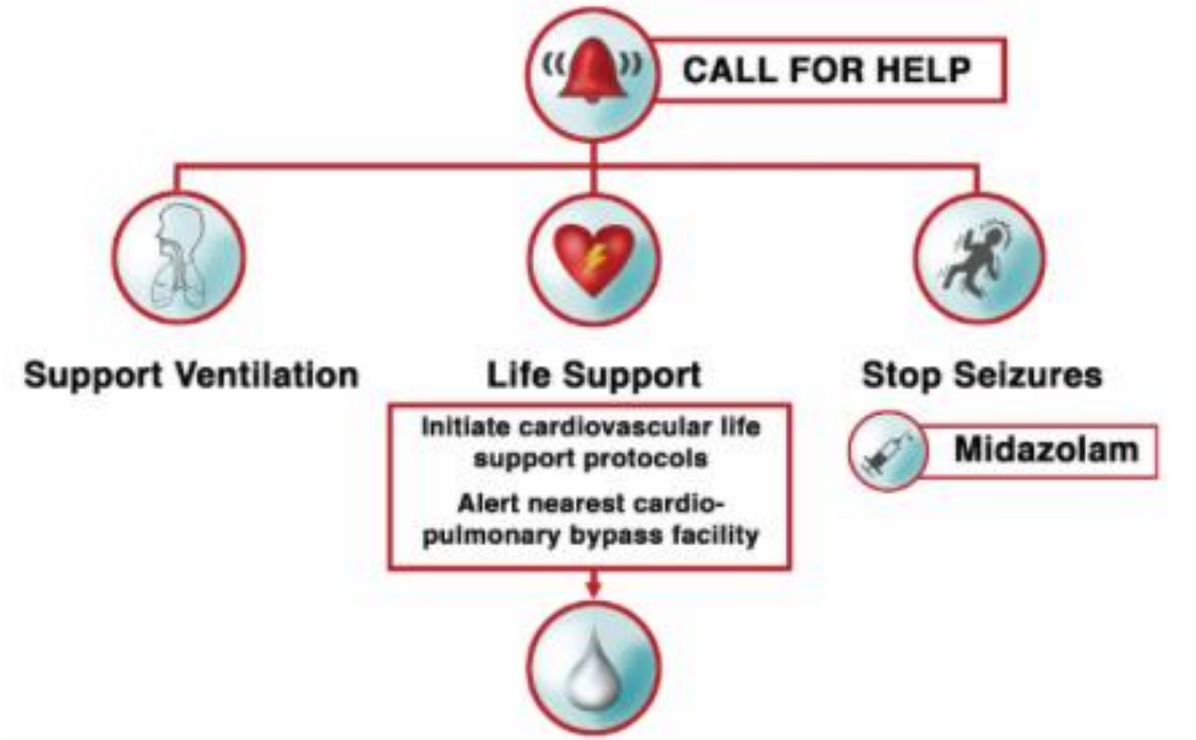
Box B: CRITICAL CHANGES

If cardiac arrest, continue lipid emulsion and → 2-1

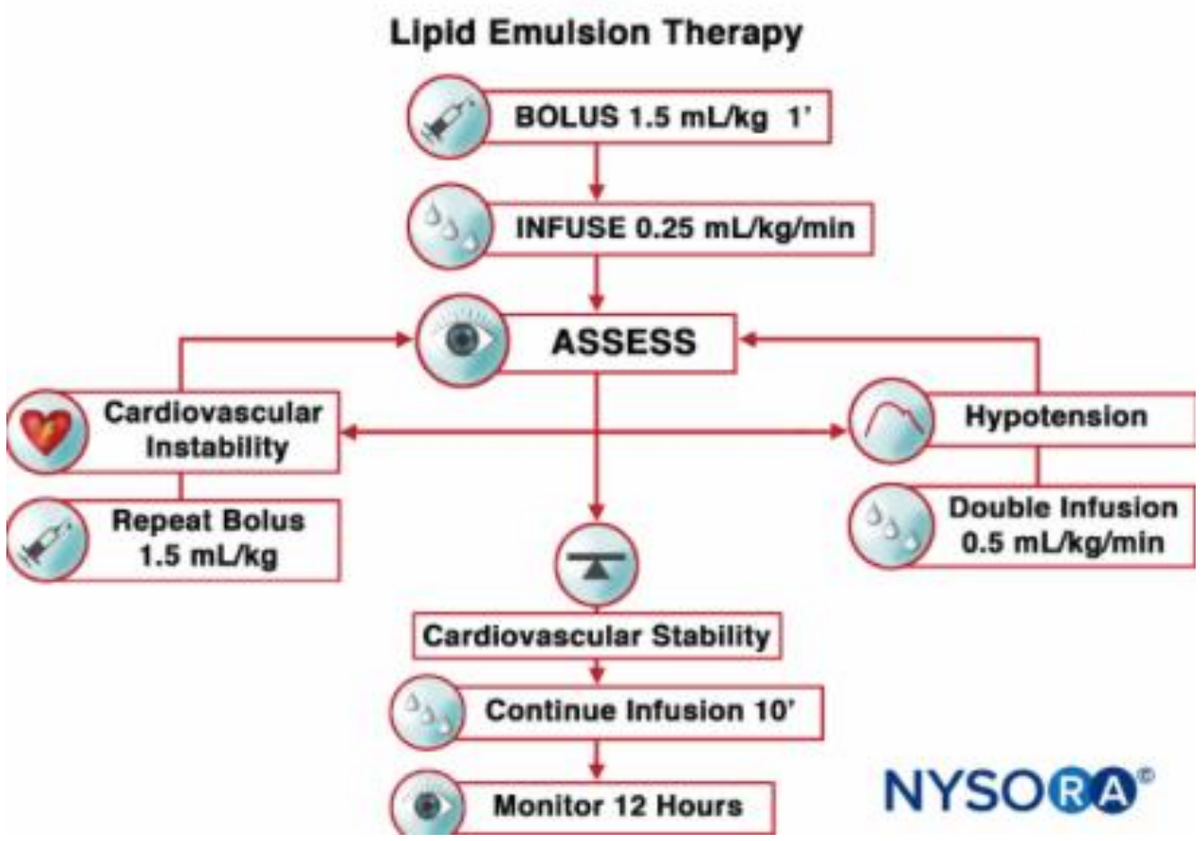
Box C: AFTER THE EVENT

Arrange safe transfer to appropriate clinical area
Exclude pancreatitis: regular clinical review, daily amylase or lipase
Report cases to MHRA: https://yellowcard.mhra.gov.uk/

Local Anesthetic Systemic Toxicity



Lipid Emulsion Therapy



Questions?