Local anaesthetic systemic toxicity (LAST)

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Incidence

LAST is a life-threatening adverse event

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
2.7 per 10 000 currently

Epidural anaesthesia:

1.2–11 per 10 000 in 1993-1997

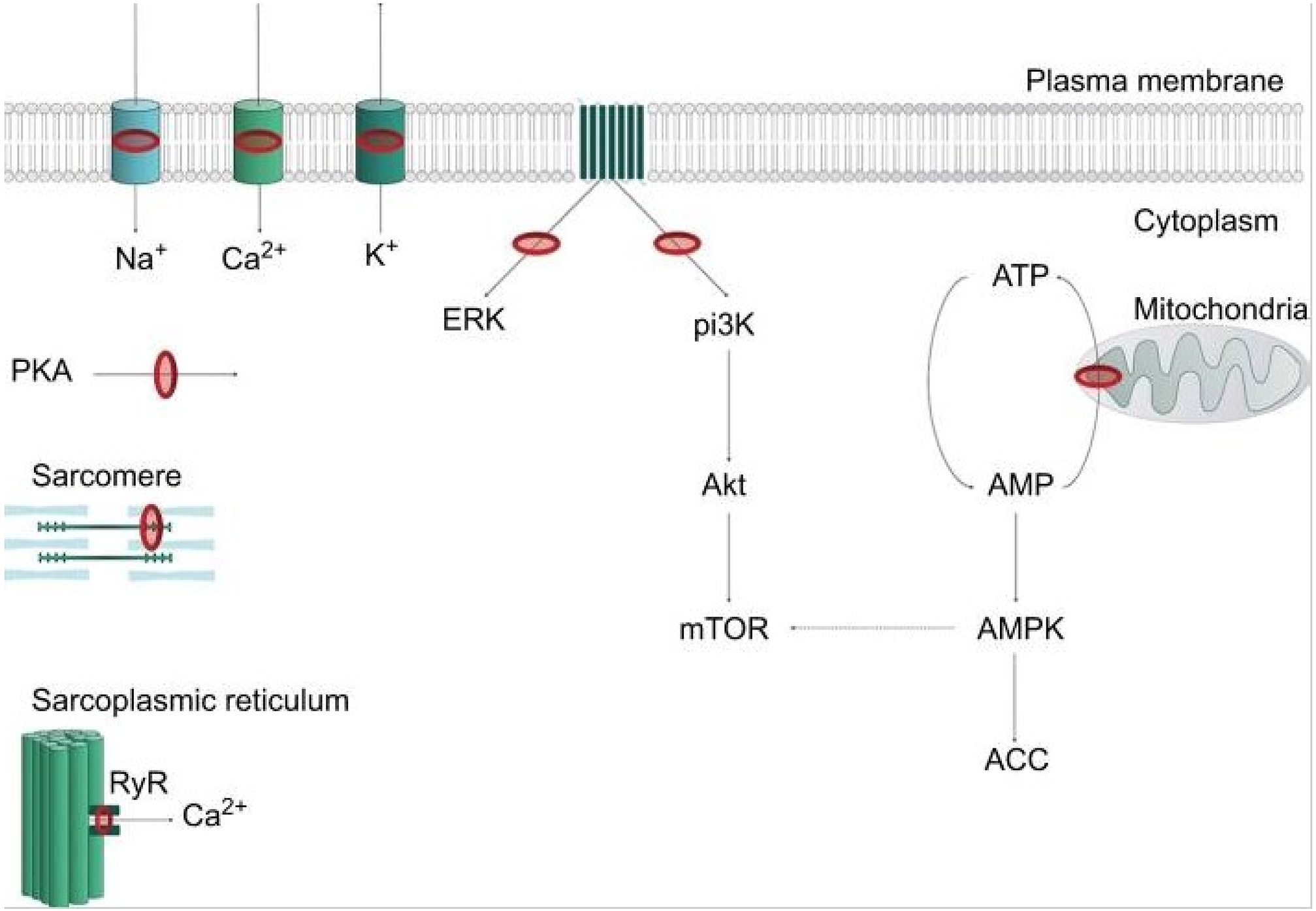
Mechanism of action

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.

pH effect on baroreceptors control mechanism.

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
  Lower ratio - more cardio-toxic (Bupivacaine)
  Higher ratio - greater safety margin (Ropivacaine, Levobupivacaine, Lidocaine).

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

Age
Extremes of age.

Neonates - reduced plasma concentrations of binding protein and immature hepatic enzyme systems - ↑ free fraction of LA.
Reduce dose by 15% in patients <4 months of age.

Elderly patients have reduced clearance of LA - ↑ the potential of drug accumulation.
Multiple comorbidities, reduced skeletal muscle mass.
Dose reduction of 10%–20% in these patients.

Pregnancy
Reduced plasma concentrations of α1-acid glycoprotein and an increased cardiac output - rapid absorption and higher peak free LA concentrations.
Doses recommended to be reduced.

Renal disease
Hyperdynamic circulation and reduced clearance of LAs, but increased α1-acid glycoprotein concentration.
Dose unchanged unless uremic with metabolic acidosis.

Cardiac disease
Less cardiotoxic drugs (ropivacaine, levobupivacaine) recommended.

Hepatic dysfunction
No change in dose needed.

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:
  - cardiovascular stability has not been restored or
  - an adequate circulation deteriorates

At any time after 5 minutes:

- Double the rate to 30 $ml.kg^{-1}.h^{-1}$ if:
  - cardiovascular stability has not been restored or
  - 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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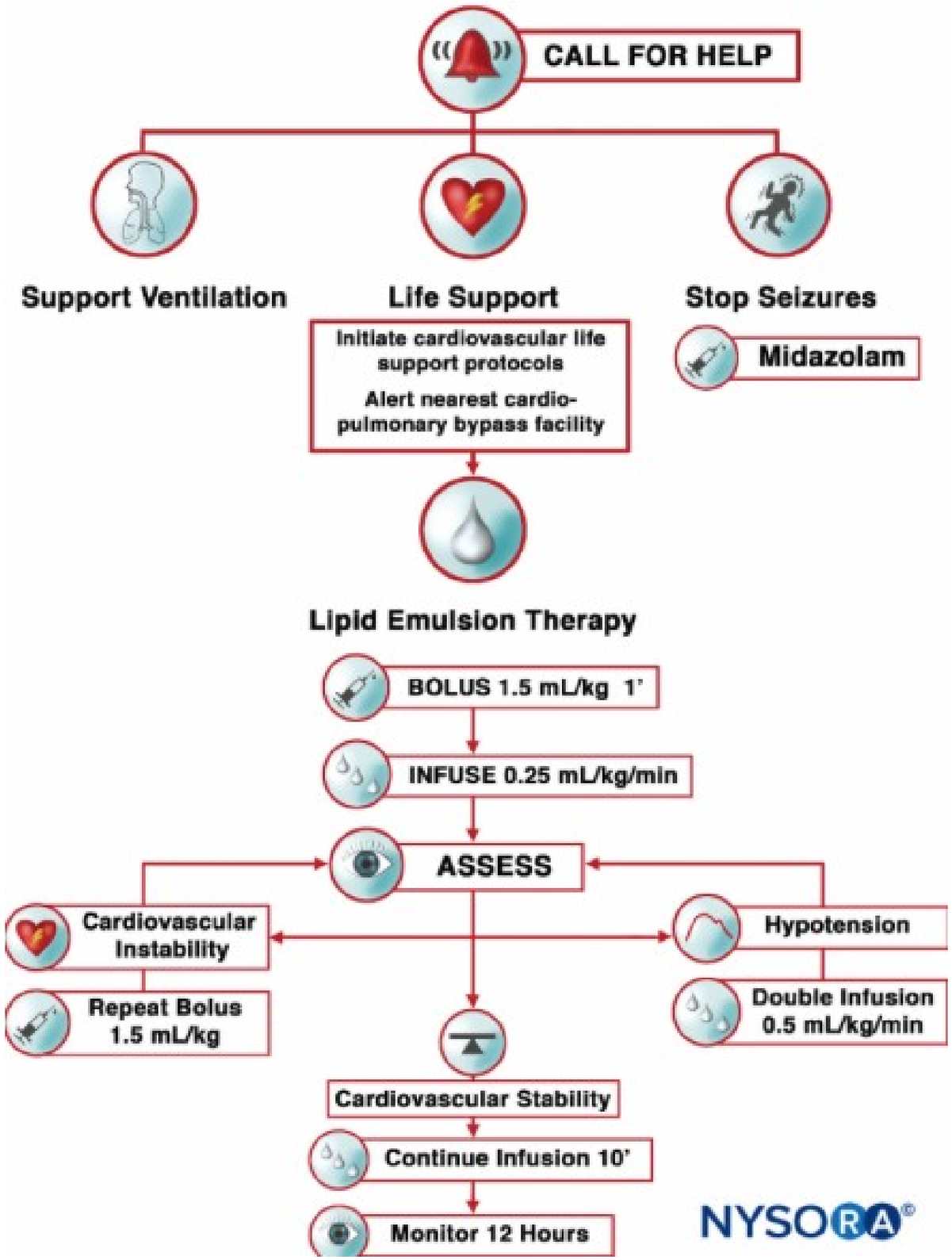
Box B: CRITICAL CHANGES

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



NYSORA Tips

- There is a greater likelihood for LA systemic toxicity in petite patients (small muscle mass), those at the extremes of age, and patients with preexisting heart disease or carnitine deficiency.
- Roughly half the cases of LAST are atypical, with no seizures (other CNS symptoms), only CV toxicity or delayed onset.
- The incidence of toxicity increases with injections near richly vascular areas. It is highest with paravertebral injections, followed by upper and lower extremity PNBs.
- Prevention of LAST-related morbidity requires optimizing a complete system for regional anesthesia: patient selection, nerve block choice, drug and dose, complete monitoring and use of USGRA when possible, and preparing for LAST by having a kit available and practicing with simulation.
- Prevention also includes raising awareness and educating our non-anesthesiology colleagues about proper use of LAs and risks, including management of LAST.

Questions?