Systemic toxic effects of local anaesthetics

Heather N Sheppard
Ravi Anandampillai

Abstract

Local anaesthetics are widely used in the provision of local/regional anaesthesia and the management of acute and chronic pain. Their mechanism of action temporarily inhibits voltage gated sodium channels in neuronal plasma membranes. Local anaesthetic systemic toxicity (LAST) is a serious yet largely preventable complication that can occur by any of the multiple routes of administration. LAST predominantly affects the central nervous and cardiovascular systems. Awareness of LAST and vigilance during administration of local anaesthetics may help in early recognition and successful management of the toxicity. Intralipid emulsion (ILE) infusions have been successfully used in reversing local anaesthetic-induced cardiotoxicity. Since 2007 in the UK, ILE infusion has been incorporated into the safety guidelines for management of LAST.

Keywords Bupivacaine; levobupivacaine; lidocaine; lipid emulsion; local anaesthetics; ropivacaine; toxicity

Royal College of Anaesthetists CPD Matrix: 1B04, 2G04

Learning objectives

After reading this article, you should be able to:

- understand the risk factors which increase the likelihood of local anaesthetic systemic toxicity
- be able to identify risk factors on an individual patient basis to prevent adverse events from local anaesthetic administration
- be able to recognize the initial signs and symptoms of LAST and its sequelae
- understand the key points in treatment and management of systemic toxicity
- appreciate recent developments in the understanding of the mechanism of action of lipid emulsion in the treatment of toxicity

Local anaesthetics (LAs) reversibly block nerve fiber conduction at an intracellular level, temporarily preventing the transmission of nociceptive signals from the anatomical region supplied by a specific nerve or plexus. Individual local anaesthetics vary in their physicochemical characteristics resulting in differing rates of onset, duration of action, potency and toxicity. If a significant concentration of a local anaesthetic agent accumulates within the systemic circulation, a potentially life-threatening adverse reaction can occur. Although now a rare event, local anaesthetic systemic toxicity (LAST) may occur whenever a significant bolus or infusion of local anaesthetic is used and typically presents within the first few minutes following administration due to inadvertent intravascular drug administration or may be delayed, resulting from more gradual systemic absorption of a toxic dose.

Mechanism of action and causation of toxicity

With the exception of benzocaine, all local anaesthetic agents have analogous structural features. They are weak bases (pKa 7.7 −8.4), consisting of a lipophilic aromatic ring component linked via an ester or amide grouping to a basic amine containing side chain.[1] The concurrent hydrophobic and hydrophilic properties of this structure allow local anaesthetics to cross the cell membrane in their unionized form with ease. In the intracellular space they dissociate and block the voltage-gated fast sodium channels, preventing the rapid early depolarization phase of an action potential from occurring. Toxicity occurs when the serum concentration of an anaesthetic agent reaches a level that affects organs dependent on sodium channel conduction, notably excitable neural tissue within the heart and CNS. Similarly to the effect exhibited in the peripheral nerves, progressive inhibition of function occurs. The presentation of LAST varies from mild prodromal symptoms (described later) to more severe and even life-threatening seizures and cardiac arrest.[2]

Toxicity may arise from:

- direct intravascular injection of local anaesthetic
- rapid or delayed absorption of an agent injected into a highly vascularized tissue
- exceeding the stated maximum safe dose of local anaesthetic.

Factors influencing the development of LAST

Numerous factors have been identified which 'influence the likelihood and severity of LAST, including individual patient risk factors, concurrent medications, location and technique of block, specific local anaesthetic compound, total local anaesthetic dose (the product of concentration and volume), early detection, and adequacy of treatment'.[3]

Pharmacokinetic considerations

When local anaesthetics are delivered peri-neurally, they are absorbed into the systemic circulation. The rate of absorption is influenced by the vasculature of the surrounding tissues and the quantity of LA. Upon reaching the plasma, the LA is rapidly redistributed to well perfused organs such as the heart, lung, liver and brain as opposed to muscle and adipose tissue.

Within the systemic circulation, LAs tend to bind to plasma proteins thereby limiting the portion of free drug available for metabolism. They have an affinity primarily towards α-1-acid glycoproteins (AAG) which constitute 1−3% of plasma protein.[4] Once the α-1-acid glycoproteins are saturated, residual drug can bind to albumin. The extent of plasma protein binding

Heather N Sheppard *MBCHb BSc(Hons) is a Foundation Doctor at NHS Tayside, UK. Conflicts of interest: none declared.*

Ravi Anandampillai *MBBS MD FCAI EDRA is a Consultant Anaesthetist at NHS Tayside, UK. Conflicts of interest: none declared.*

influences both the duration of local anaesthetic action and the rate of uptake by surrounding tissues. Bupivacaine has a higher percentage of protein binding and a longer duration of action than lidocaine, which may explain the increased cardiotoxicity and notoriously refractory cardiac arrhythmias observed in bupivacaine-induced LAST. Once plasma protein binding is saturated, the level of free drug in the systemic circulation will rise rapidly, leading to the sudden onset of symptoms associated with severe, life-threatening toxicity. Plasma levels of α-1-acid glycoproteins and thus local anaesthetic uptake is affected by pregnancy, burns, hepatocellular pathologies, drug interactions and notably in patients treated for HIV.[4] The AAG levels may fall in these circumstances leading to a higher plasma concentration of free drug and thus amplifying the risks of LAST.

Metabolism is dependent upon the specific chemical structure of the individual anaesthetic agent used, esters are hydrolysed by cholinesterases in the plasma and amides are metabolized by hepatic amidases. Any cause of hepatic dysfunction and/or reduced perfusion will lead to a decrease in the rate of local anaesthetic metabolism. A patient who is hypoxic, hypercarbic and acidotic will accentuate the effects and increase the likelihood of adverse outcomes associated with toxicity.

These metabolites, plus an estimated 5% of local anaesthetics in their unchanged form, are renally excreted. Factors affecting elimination include patient's age, renal function and physiological status. For example, in uraemic patients, the presence of a hyperdynamic circulation leads to a greater rise in plasma concentrations of LAs, however, this is partially offset by an increase in plasma AAG concentrations.

Non-pharmacological considerations

Aside from the pharmacological aspect, numerous individual patient factors influencing the risk of developing LAST should be considered prior to LA administration. Patients with decreased muscle mass including neonates, infants, frail and elderly patients are known to have prolonged elimination times and are at higher risk of developing LAST. Female patients are at higher risk of toxicity than male patients, with the risk being further increased in pregnancy. This is because progesterone increases the sensitivity of axons to the effects of local anaesthetics. Metabolic disorders, low plasma protein binding states and the nutritional status of the patient can influence the risk and severity of toxicity[3] due to changes in total body water and volume of distribution. This along with nutritionally induced changes in AAG levels can influence the plasma concentration of local anaesthetics. The risks and severity of LAST are directly related to the levels of unbound free drug and increased elimination times.

Signs and symptoms of LAST

The development of local anaesthetic systemic toxicity follows an evolution of signs and symptoms, attributable to progressive toxicity within the CNS and cardiac tissue.

CNS toxicity

Lipophilic local anaesthetic agents cross the blood brain barrier with ease. Early excitatory symptoms arise from blockade of cortical inhibitory pathways and include nervousness, confusion, agitation, tinnitus, visual disturbance, paraesthesia, peri-oral tingling and muscle fasciculation. Seizures within the context of LAST usually take the form of generalized tonic-clonic seizures and are followed by CNS depression, decreased conscious level and respiratory arrest. CNS toxicity does not always follow such a well-defined pattern and CNS depression may be the first indication of toxicity, particularly in patients who may be taking CNS depressants such as benzodiazepines. In contrast, hypercarbic patients are at risk due to elevated $PaCO_2$ which reduces the seizure threshold but concurrently increases cerebral vasodilatation/cerebral blood flow and delivery of LA to the CNS.

Cardiac toxicity

Local anesthetics have a diverse range of biochemical effects on cardiac tissue; ion channel blockade, inhibition of oxidative phosphorylation in mitochondria leading to decrease in electron transport and ion uncoupling. This leads to a reduction in systemic vascular resistance, cardiac conduction and myocardial contractility. Ion channel blockade within cardiomyocytes shortens the refractory period of cardiac action potentials leading to conduction defects, with prolongation of both PR and QRS intervals classically observed on ECG. Hypotension, tachycardia and arrhythmias ensue, progressing to severe hypotension, bradycardia and ultimately cardiac arrest. Furthermore, evidence has shown that cardiac arrest induced by LAST is resistant to the usual methods of resuscitation.[5]

Prevention

The old adage *prevention is better than cure* is undoubtedly the preferred convention when it comes to LAST. Recognition of previously discussed risk factors and consideration of these on an individual patient basis before any administration of local anaesthetic agent is of key importance. No single intervention can prevent systemic toxicity and a summary of the list of

Recommended interventions in the prevention of local anaesthetic systemic toxicity (LAST)

- The use of ultrasound guidance, particularly when administering a peripheral nerve block
- Correctly calculating and administering the lowest effective dose
- Gentle aspiration immediately prior to each injection to reassure not in intravascular space
- Administer anaesthetic agents incrementally in 3–5 ml aliquots, pausing after each aliquot
- Intravascular markers are recommended when the doses needing to be administered are potentially toxic.
- Intravascular injection of epinephrine (dose adjusted for adults and children respectively) which increases systolic blood pressure by $\geq$15 mmHg
- Awareness of cumulative nature of local anaesthetic agents when multiple doses or agents are being administered by different members of a perioperative team
- On administering a truncal block, dose according to lean body weight, use adjunctive epinephrine and the patient should be observed for up a minimum of 30 mins post administration.
- Highlight local anaesthetic dosing concerns/limits at the surgical pause

Box 1

recommendations is presented in Box 1. Perhaps the most notable is to avoid injecting local anaesthetic agents intravascularly. Ultrasound guidance does not eliminate but greatly reduces the risk of intravascular administration by allowing the visualization of needle tip position and the dissipation of local anaesthetic within the tissues around the target. Gentle aspiration of the needle (to detect vascular puncture) prior to injection should be performed to provide reassurance of correct positioning, acknowledging that it is associated with an approximate 2% false negative rate.

Treatment

While management of LAST is in the first instance largely supportive, successful treatment is reliant on interventions which reverse the underlying causative principles of toxicity.

1. **Discontinue injection or infusion** of the anaesthetic agent immediately.
2. **Airway management:** a patent and protected airway is vital in preventing hypoxia, hypercapnia and the resultant acidosis which as previously discussed accentuates the effects of toxicity. If there is decline in consciousness level then tracheal intubation is indicated.
3. **Lipid emulsion** is indicated in the treatment of severe toxic reactions – it *must* be given if there is circulatory arrest and considered in the absence of circulatory arrest if signs of severe toxicity exist (e.g. altered conscious level or mental state, seizures or cardiovascular collapse).

Although initially developed for parenteral nutrition, intravenous lipid emulsion has been used as a rescue treatment for LAST for over a decade, with notable case reports of successful outcomes, particularly in the context of bupivicane-induced toxicity. Evidence, largely in the form of peer-reviewed case reports, suggests that lipid emulsion shows optimal efficacy when administered at the earliest opportunity after toxicity has been recognized.[3,5] '*The commercial preparation Intralipid 20% is manufactured by Fresenius Kabi; 1 liter consists of 200 g purified soybean oil, 12 g purified egg phospholipids, and 22 g anhydrous glycerol, and it is a source of omega-3 and -6 essential fatty acids with total energy content 8.4 MJ (2,000 kCal).*'[6] In the UK it is currently recommended that 1000 ml of 20% lipid emulsion should be readily accessible in

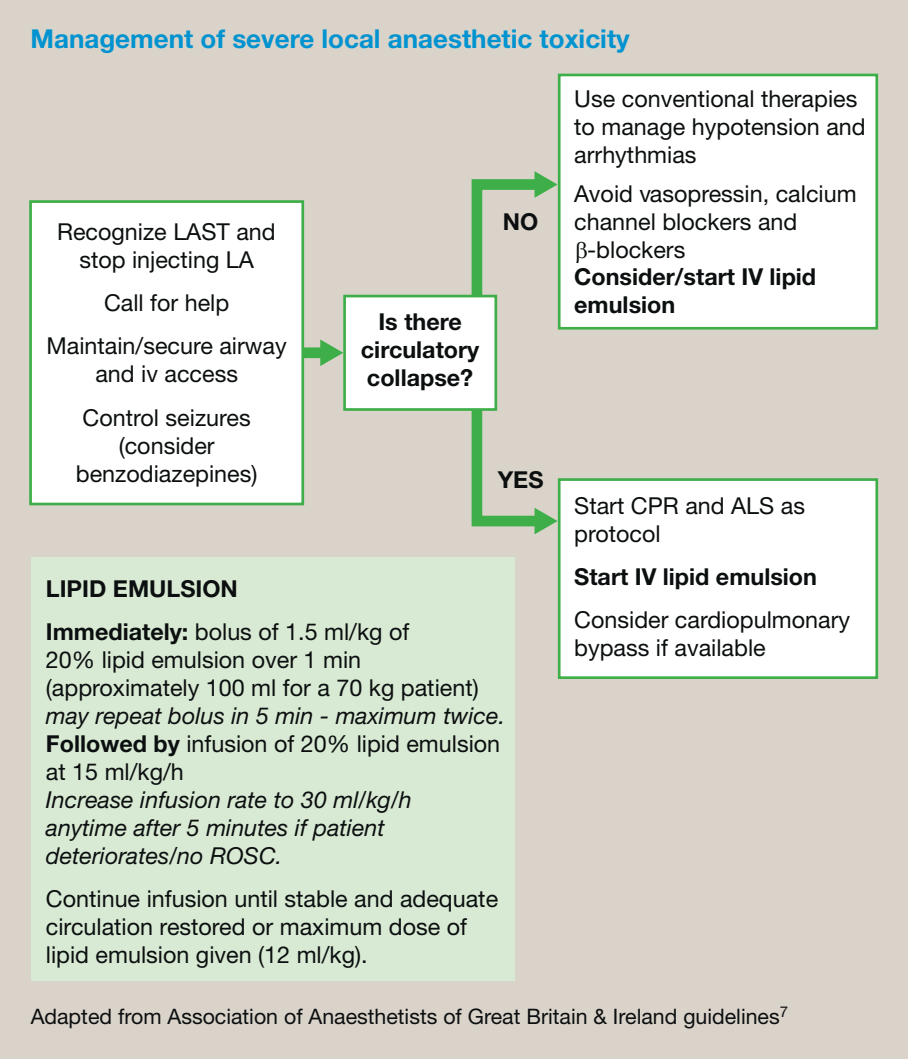

Figure 1

clinical areas where significant concentrations of local anaesthetic agent are being administered. Cumulative doses of lipid emulsion should not exceed a maximum of 12 ml/kg.[7] The reversibility of LAST by use of lipid emulsion is not completely understood and is thought not to be attributable to a single mechanism but rather an interplay of multiple complex processes.

Lipid emulsion causes expansion of the intravascular lipid phase, driving the equilibrium such that the local anaesthetic agents move from tissue to plasma and into the lipid thus draining and retaining the free unbound anaesthetic agent alongside scavenging it from tissues.[5] However, pharmacokinetic analysis has shown the level of anaesthetic sequestering by what has historically been named the 'lipid sink' is not of a level that would account for the reversal of LAST, thereby supporting the existence of other mechanisms of action.[8]

Recent hypotheses have revised the term to 'lipid shuttling' to encompass several mechanisms by which intravascular lipids work to aid the treatment of LAST and three main contributory processes have been identified. The first is this 'lipid sink' phenomenon which is no longer thought to be a static sink but rather a dynamic process that steals lipophilic molecules from highly vascular organs such as the heart and delivers them to organs that store and further metabolize the drug, namely the liver and musculature.[9] Second is the effect attributed to expansion of the intravascular volume by the administration of the lipid emulsion. This volume expansion counters, to some extent, the profound vasodilation caused by LAST and also increases the preload and the end diastolic ventricular volume. Altogether these mechanisms improve cardiac output and blood pressure. Finally, the cardiotonic effect has a duplex approach, primarily the lipid emulsion provides substrate for direct energy delivery to the myocardium and this improves cardiac function. Secondary to this, intravascular lipid increases calcium concentrations within the cardiac tissue by its effect on calcium ion channels via long chain fatty acids resulting in a positive ionotropic effect which improves cardiac function. A recent mechanistic study by Fettiplace et al. provided further support for this 'lipid shuttling' theory.[10]

Recent evidence demonstrates that the ionotropic benefit of lipid emulsions is only seen when the concentration of local anaesthetic agent in the myocardial tissue is less than that associated with ion channel blockade. As such it follows that maintaining good coronary perfusion, by effective cardiopulmonary resuscitation, will aid reduction of anaesthetic concentration within the myocardium and optimize the efficacy of the lipid rescue. Formalized guidelines on the use of lipid emulsion have been published by the Association of Anaesthetists of Great Britain & Ireland. Treatment for an average patient weighing 70 kg based on these guidelines is summarized in Figure 1.[7]

4. **Seizures** should be treated promptly with benzodiazepines or small boluses of propofol in addition to lipid rescue. Note that propofol should be used with caution if there are signs of cardiovascular compromise.
5. **Cardiac arrest:** In the event of cardiac arrest, local CPR protocols should be followed and concomitant lipid emulsion rescue initiated. However, it is advised that if epinephrine is administered it should be in small doses (1 μg/kg). Vasopressin, calcium channel blockers and beta-blockers should be avoided as they have an additive myocardial depressant effect.

If despite treatment the patient fails to respond, particularly to lipid rescue, then consideration should be given to cardiopulmonary bypass if this is readily available. ◆

REFERENCES

1 Becker D, Reed K. Essentials of local anesthetic pharmacology. *Anesth Prog* 2006; **53:** 98–109.
2 Gitman M, Barrington M. Local anesthetic systemic toxicity. *Reg Anesth Pain Med* 2018; 1.
3 Neal J, Barrington M, Fettiplace M, et al. The third American society of regional anesthesia and pain medicine practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med* 2018; **43:** 113–23.
4 Urien S, Brée F, Testa B, Tillement J. pH-dependency of basic ligand binding to α1-acid glycoprotein (orosomucoid). *Biochem J* 1991; **280:** 277–80.
5 Ciechanowicz S, Patil V. Lipid emulsion for local anesthetic systemic toxicity. Anesthesiology Research and Practice, 2012; 1–11. 2012.
6 Ok S, Hong J, Lee S, Sohn J. Lipid emulsion for treating local anesthetic systemic toxicity. *Int J Med Sci* 2018; **15:** 713–22.
7 Aagbi.org. (2018). [online] Available at: https://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf (Accessed 2 Jul 2018).
8 Kuo I, Akpa B. Validity of the lipid sink as a mechanism for the reversal of local anesthetic systemic toxicity. *Anesthesiology* 2013; **118:** 1350–61.
9 Fettiplace M, Lis K, Ripper R, et al. Multi-modal contributions to detoxification of acute pharmacotoxicity by a triglyceride microemulsion. *J Contr Release* 2015; **198:** 62–70.
10 Fettiplace M, Weinberg G. The mechanisms underlying lipid resuscitation therapy. *Reg Anesth Pain Med* 2018; **43:** 138–49.

