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Local anaesthetic systemic toxicity

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Key points

- Any unusual cardiovascular or neurological signs, including outright cardiac arrest, after local anaesthetic (LA) administration should raise suspicion of local anaesthetic systemic toxicity (LAST).
- The risk of LAST is influenced by patient factors, the site and conduct of the block, and the LA type and dose.
- There are pre-, intra-, and post-procedure measures to reduce the risk of LAST.
- Education of anaesthetists and non-anaesthetists in LAST management should improve patient safety.
- AAGBI guidelines aid emergency management of LAST.

Well-placed local anaesthetics (LAs) can yield great clinical benefits. But systemic toxicity related to their use can be devastating. The highly publicized case in 2004 of Mayra Cabrera, a theatre nurse who died shortly after delivery of her baby boy when her epidural infusion of bupivacaine was mistakenly connected to her i.v. line, reminds us to be vigilant and to learn from such rare events. While prevention is clearly the most important element in avoiding morbidity and mortality associated with local anaesthetic systemic toxicity (LAST), such cases still occur despite best practice. Knowing how to manage these uncommon events is vital.

In this review, we cover LA toxicity, its incidence, clinical features, risk factors, prevention, and management and examine i.v. lipid emulsion (ILE) therapy in more detail.

Incidence

LAST has been recognized for more than a hundred years, but the precise incidence is currently unknown. In 1928, the American Medical Association reported 40 deaths attributable to LAs.[1] Cocaine was responsible for half of these deaths, but procaine was also implicated. These findings prompted the search for less toxic agents. Lidocaine, first synthesized in 1944, was the first amide LA to be used clinically. However, in 1979, the potentially fatal toxicity of amide LAs was highlighted by Albright.[2] More recently, studies from 1993 to 1997 reported a rate of LAST for epidural anaesthesia of 1.2–11 per 10 000 anaesthetics.[3] The rate of LAST for peripheral nerve block was reported as 7.5 per 10 000 in 1997, 2.5 per 10 000 in 2004,[4] 9.8 per 10 000 in 2009,[5] and when using ultrasound 8.7 per 10 000 in 2013.[6]

The National Audit Project 3 (NAP3), by the Royal College of Anaesthetists, investigated the major complications of central neuraxial block (http://www.rcoa.ac.uk/system/files/CSQ-NAP3-Full_1.pdf). Eleven cases of wrong-route administration in the UK over a 1 yr period were identified, six involving i.v. bupivacaine injection.

Types of toxicity

LA toxicity may be local or systemic.

Local

These include a localized allergic reaction to *para*-aminobenzoic acid (an ester metabolite), myotoxicity, neurotoxicity (cytotoxicity), and transient neurological symptoms.[7]

Systemic

Neurological/cardiovascular: LAST

LAST, the main focus of this article, comprises neurological and cardiovascular features. The earliest descriptions of LAST in 1887

highlight several of its prominent clinical features, namely respiratory failure, seizures, palpitations, and 'irregular heart action'.[8]

After LA administration, any abnormal cardiovascular or neurological symptoms and signs, including isolated cardiac arrest, should raise suspicion of LAST. The presenting features of LAST vary widely. Importantly, cardiovascular collapse may occur without preceding neurological changes. Furthermore, clinicians must remain vigilant as LAST may occur some time after the initial LA administration, potentially in an environment where the patient is less well monitored.

Central nervous system toxicity is classically described as a two-stage process. An initial excitatory state is followed by a depressive phase. Early neurological features include perioral tingling, tinnitus, and slurred speech. Lightheadedness and tremor may also occur, as may a change in mental status with confusion or agitation. However, LAST can occur without these characteristic premonitory signs. The excitatory neurological phase culminates in generalized convulsions. This may lead to the depressive phase of coma and respiratory depression.

Cardiovascular system toxicity is classically in three phases. The initial phase includes hypertension and tachycardia. The intermediate phase is associated with myocardial depression and hypotension. The terminal phase includes peripheral vasodilatation, severe hypotension, and a variety of arrhythmias such as sinus bradycardia, conduction blocks, ventricular tachyarrhythmias, and asystole.

Anaphylaxis

Although anaphylaxis to LA is very uncommon, it is more likely to occur with esters than amides. Methyl-paraben or metabisulphites are preservatives that may be the cause in some cases. Some previously reported reactions may have actually been anaphylaxis caused by latex or the cardiovascular reactions to systemically absorbed epinephrine being misinterpreted as anaphylaxis.

Methaemoglobinaemia

Methaemoglobinaemia can occur with prilocaine due to its metabolite, *o*-toluidine. Eutectic mixture of local anaesthetic cream should be avoided in patients with congenital or idiopathic methaemoglobinaemia or those <1 yr old receiving methaemoglobinaemia-inducing drugs such as sulphonamides, phenytoin, or benzocaine.

Mechanisms of toxicity

LA reaches the circulation via systemic absorption or accidental intravascular injection. Accidental i.v. injection is more common than arterial injection, can occur during any regional anaesthetic, and results in rapid onset of symptoms and signs of toxicity. Systemic absorption normally has a delayed onset.

Despite decades of research, the mechanism of LAST remains elusive.[9] Lipophilic LAs rapidly cross cell membranes and toxicity reflects action at a large number of sites including ionotropic, metabotropic, and other targets. In the brain, LA affects the balance between inhibitory and excitatory pathways.

In the heart, LAs can cause conduction blocks through effects on sodium, potassium, and calcium channels. These alone might cause dysrhythmia and reduce contractility. But excess LA may have more widespread effects still: it can disrupt intracellular signals originating at metabotropic receptors, leading to reduced cyclic adenosine monophosphate concentrations and thence reduced contractility. Moreover, the heart has a predilection for fats (and ketone bodies). To be oxidized, the fats' acyl parts must be carried across the mitochondrial membranes by a translocase system which may also be inhibited by clinically relevant concentrations of LA.

Risk factors for toxicity

These relate to the LA, the block, and the patient.

LA-related

The type and dose of LA injection influence toxicity risk.

Type of LA

LA agents are short-, moderate-, or long-acting esters and amides. Cocaine is a short-acting ester, lidocaine a moderate-acting amide, and bupivacaine and ropivacaine are long-acting amides.

The standard formulation of bupivacaine is the racemic mixture of the *S*- and *R*-enantiomer, whereas levobupivacaine comprises only the *S*-enantiomer. In perfused rabbit hearts,[10] more levobupivacaine than bupivacaine was required to induce cardiac arrest. In sheep,[11] levobupivacaine caused fewer convulsions and arrhythmias than bupivacaine, at similar doses. Ropivacaine may cause less motor block, but whether it is clinically significantly less toxic is unknown. Indeed, it is not clear that any one agent is less toxic than another to a degree that is clinically relevant.

LAs have different intrinsic vasoactive effects. Levobupivacaine and ropivacaine have intrinsic vasoconstrictor properties that may prolong duration of action and slow systemic absorption. This may be safer than bupivacaine, an intrinsic vasodilator, but the clinical significance of this difference remains unclear.

An important concept in the study of LAST is the ratio of the dose required to produce cardiovascular collapse to that required to induce seizures, the so-called CC/CNS ratio. Bupivacaine has a CC/CNS ratio of 2.0 compared with 7.1 for lidocaine. Therefore, progression from CNS signs and symptoms to cardiovascular collapse can occur more readily with bupivacaine than with lidocaine.

Dose of LA

Determining the optimal dose of LA to use is complex. It is self-evident that the lowest effective dose should be used. Patient characteristics need to be considered and also the site of administration. Pragmatists may argue that the recommended doses provide a rough guide for clinical use. An alternative view is that the maximum weight-based doses have no rational basis as such dosing does not correlate to the resulting blood level and does not take into account relevant patient factors or the site of injection. Moreover, they vary significantly between different texts and different countries, are not based on solid evidence, and might be too high for some patients.[12] For instance, it is not specified whether the maximum doses are based on actual or ideal body weight. As a result, if dosing is calculated on actual body weight, the obese, pregnant, or both patients may receive a dangerously high dose. Furthermore, such hard and fast dosing rules do not take into account the complete clinical context. Nevertheless, it is reasonable to use some standard as a starting point for deciding on a dose. For this reason, the values in Smith and colleagues,[13] 4th edition, are quoted in Table 1. The particulars for a given block (e.g. surgical site and duration, planned site of injection, size, and co-morbidities of the patient) must be

Table 1 Maximum doses of LA. All parameters are from Smith and colleagues[13] with the exception of ropivacaine.[14] (Of note, epinephrine slows systemic absorption, prolonging the duration and intensity of the block while limiting peak plasma concentrations)

	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	—

considered in selecting the final dose. Notably, Barrington and Kluger found that small size is a risk factor for LAST.

Block-related

Site of block

The site is important since some sites have a higher risk of direct intravascular injection (e.g. interscalene or stellate ganglion block) and others carry an increased risk of rapid absorption and toxicity due to the injection being in a highly vascularized area (e.g. scalp, bronchial mucosa, or pleura). The classic order of sites' propensities to lead to toxicity, in order from lowest to highest: subcutaneous injection, brachial plexus, epidural, caudal, and finally intercostal blocks and topical anaesthesia.

Single administration vs continuous infusion

Continuous infusions can cause accumulation of LA in blood and tissue and so lead after delay to LAST. Vigilance for LAST some time after initial administration is therefore necessary and should be continued at some level throughout the period of infusion.

Conduct of the block

The factors that should decrease the risk of toxicity while the block is being performed are:

- frequent aspiration,
- incremental injection,
- test dose,
- tracer, e.g. epinephrine (controversial),
- ultrasound-guided needle placement.

Patient-related factors

General principles

Toxicity relates to the free peak plasma concentration. Increased perfusion at the site of injection raises the peak plasma concentration by accelerating systemic absorption; a low α_1-acid glycoprotein (AAG) titre results in a higher concentration of free LA. A reduction in the clearance leads to accumulation with repeated doses and infusions.

Co-morbidities (renal, liver, and cardiac disease)

Patients with severe renal impairment typically have a hyperdynamic circulation, a reduced clearance of LAs, but an increased AAG concentration. Overall, these may slightly increase toxicity risk. It is recommended that the initial dose be reduced (by 10–20% according to the degree of renal impairment).

In patients with liver disease, LA clearance is reduced. Single-dose blocks are unaffected, but the doses for repeat boluses and continuous infusions should be reduced. Such patients may also have renal or cardiac disease. AAG is still synthesized in patients with end-stage liver disease, offering some protection against LAST.

Patients with severe cardiac failure are particularly susceptible to LA-induced myocardial depression and arrhythmias. Further, lower liver and renal perfusion slows metabolism and elimination, so safe initial and maintenance doses of LA are correspondingly lower too. On the other hand, poor perfusion at the injection site may decrease peak plasma concentrations. Finally, if circulation time is prolonged, the likelihood increases that injections could be misplaced before a tracer (e.g. epinephrine) indicates an intravascular injection.

Elderly patients

Reduced blood flow and organ function lowers clearance, risking toxicity with infusions, or repeat doses. Moreover, elderly patients frequently have multiple co-morbidities altering LA pharmacokinetics and pharmacodynamics. Furthermore, nerves appear more sensitive to LA block because of a reduction in axonal function, altered nerve morphology, and reduced surrounding fatty tissue. In combination, all these factors suggest there is a safety benefit in dose reduction without reducing clinical efficacy.

Paediatric patients

Neonates and infants have reduced AAG levels; indeed, the plasma concentration of AAG at birth is about half that of an adult. Children have an increased elimination half-life of LAs, which in neonates is increased to 2–3 times that of an adult. This increases the risk of accumulation with continuous infusions.

Pregnant patients

Pregnant patients are at an increased risk of toxicity. They have lower AAG levels; meanwhile, accelerated perfusion of sites of injection results in rapid absorption and a high peak free LA concentration. [In the UK Confidential Enquiry into Maternal and Child Health (CEMACH) in 2003–5, there was one death caused by i.v. administration of epidural bupivacaine. In the UK 2006–8 report (CMACE), there were no maternal deaths caused by LAST.]

Prevention

During every stage of interaction with a patient involving LA administration, prevention of LAST must be a key patient safety goal.

Pre-procedure

During preoperative assessment, evaluation of the risks and benefits of regional anaesthesia for that individual should be discussed. Patient communication should include an explanation of the procedure, which can improve the patient's co-operation during the procedure.

The environment in which the block is to occur is very important. The block should take place in a setting with monitoring as per AAGBI standards, resuscitation equipment, and capable help nearby.

During preparation for the block, syringes should be labelled appropriately and be prepared separately from any other anaesthetic drugs. The choice and dose of LA to be administered should be considered in advance. Sufficient dose to achieve an effective block should be administered, with avoidance of an excessive dose to minimize the risks of LAST. The patient's vital signs should be monitored continually during the block with AAGBI

standards of monitoring (i.e. ECG, pulse oximetry, and non-invasive arterial pressure monitoring).

Intra-procedure

The method of administering LA can reduce the risk of LAST. While frequent aspiration has been reported in cases of LAST, allowing repeated checks that the needle or catheter has not migrated intravascularly may be useful. Slower injection may reduce the peak plasma LA concentration. It could also allow earlier detection of intravascular needle placement.

The use of tracers such as epinephrine or fentanyl is controversial. Tracers may lead to false-positive results, for example, the physiological tachycardia in labour has resulted in removal of correctly placed catheters. However, there is a considered opinion that using a tracer to aid rapid recognition of an intravascular injection may increase the block's safety.

Continual communication with the patient during the procedure is useful. While this can aid detection of signs of intravascular injection such as perioral tingling or tinnitus in cooperative patients, this has to be balanced with the risks of patient movement. As a result, there may be circumstances where having the patient completely alert is inappropriate.

Ultrasound-guided regional anaesthesia is now widespread and may in itself reduce the risk of LAST.[15] Practitioners generally hold the needle still when performing landmark-guided techniques, whereas when performing the block under ultrasound, there is more needle movement and the LA is administered more widely. This may reduce but not abolish the risk of the whole dose being injected directly into a vessel. Ultrasound guidance may allow lower LA doses to be used, although such reduction has to be balanced with the risk of block failure.

The National Patient Safety Agency (NPSA) in 2009 issued a Safety Alert warning that Luer connectors common to spinal, epidural, and regional anaesthesia needles and i.v. cannulae increased the risk of wrong-route injection. The introduction of non-Luer connectors has been slow for a variety of reasons. Individual manufacturers have offered different solutions, comparison of these options has been fraught with practical difficulties, and at least one patient has been endangered due to the unforeseen incompatibility of the needles and syringes.

Post-procedure

Any peripheral nerve block catheter, epidural or spinal catheter should be labelled clearly and its presence documented on both the anaesthetic chart and the patient notes. The presence of the catheter should be communicated clearly to the nursing and medical staff responsible for ongoing patient care. Ongoing monitoring is vital as cases of delayed LAST do occur.

Management

Despite meticulous technique and adhering to best practice, LAST can still occur. It is vital to be aware of this possibility in order to diagnose and manage it appropriately.

Awareness of condition

If clinicians are unaware of the possibility of LAST, its diagnosis will be delayed or missed completely. As a consequence, prompt and appropriate treatment will not occur in the emergency situation, particularly important as the treatment of LAST differs from that of cardiac arrest from other causes. Recognition of the risk of LAST may also encourage the previously complacent or over-optimistic at least to establish monitoring and i.v. access before injecting potentially toxic doses of LA.

Anaesthetists

Just as malignant hyperpyrexia is rare, so too is LAST, so it is equally important to have a LAST-specific plan in place ahead of time. Simulation may provide experience in the management of a condition that will not be seen by the majority of anaesthetists. Immediate availability of copies of the guidelines, along with relevant drugs and administration equipment in anaesthetic rooms and theatres, may also be useful.

Non-anaesthetists

Non-anaesthetists are increasingly administering regional anaesthesia. Emergency physicians treating patients with a fractured neck of femur, for example, may perform femoral nerve blocks. While prompt analgesia is clearly advantageous, doctors performing this procedure must be aware of the risks, take the necessary precautions to minimize the risks, and know how to manage a LAST emergency. Similarly, most doctors, for a variety of indications, administer LA to patients.

AAGBI Safety Guideline

The AAGBI Safety Guideline on LAST, published in 2010, recommends the following steps:

(i) recognition (see types of toxicity above),
(ii) immediate management,
(iii) treatment,
(iv) follow-up.

Immediate management

The immediate management involves the general safety and resuscitation measures that are crucial in any emergency. First, stop injecting the LA and call for help. Then concentrate in turn on airway, breathing, and circulation. If the patient is in cardiac arrest, cardiopulmonary resuscitation (CPR) must commence. Alternatively, if the patient still has a cardiac output, 100% oxygen should be administered and the airway secured as necessary. I.V. access needs to be confirmed or established. Seizures should be addressed quickly and treatment options include a benzodiazepine, thiopental, or possibly propofol. (Propofol may well be more quickly available than the other drugs. But it may also have a more cardiodepressant effect than the alternatives. Its lipid is irrelevant.)

Cardiovascular system effects, such as arrhythmias, conduction block, and progressive hypotension and bradycardia, can be managed by conventional ALS protocols. That said, logic suggests lidocaine and other LAs should be avoided as an anti-arrhythmic; some evidence from experiments on animals suggests that epinephrine may better be used in smaller doses than in the current ALS guidelines, and that vasopressin is best avoided altogether.[16] But before definitive proof or recommendation, unswerving adherence to the guidelines (with full doses of epinephrine) will be more easily defensible.

Treatment

If the patient is in cardiac arrest, give ILE and continue CPR, remembering that recovery from an LA-induced cardiac arrest may be prolonged. (In rare circumstances, rapid institution of cardiopulmonary bypass may be possible, and then should be considered.)

If the patient is not in cardiac arrest, consider giving ILE. Propofol is not a suitable alternative as to obtain a sufficient dose of lipid would require a propofol overdose. Early administration of ILE, for example, in a patient purely with neurological signs, can attenuate neurological symptoms and prevent progression to cardiac arrest. At present, we cannot predict who will progress to cardiac arrest and who will not.

Follow-up

Patient follow-up

After the incident, the patient's clinical condition and vital signs need to be monitored in an appropriate environment, but the length of time required is unclear. Pancreatitis, a potential complication of ILE administration, cannot be detected by routine laboratory testing as the assays for amylase and lipase measure glycerol production, which is already in abundance after ILE. Abdominal CT may be required.

ILE does not interfere with sodium, potassium, chloride, calcium, bicarbonate, urea, and troponin assays. Significant interference is demonstrated with albumin and magnesium assays. Assays for amylase, lipase (as described above), phosphate, creatinine, total protein, ALT, CK, and bilirubin are all affected post-ILE. Glucose assays may sometimes be affected too; colorimetric methodology demonstrates interference, whereas potentiometry does not.[17]

Incident reporting

Local incident reporting systems should be utilized. As LAST is rare, when ILE was first administered, it was crucial to share experiences with the medical community and so www.lipidrescue.org was established. Anonymized case details can be entered. Historically, ILE administration could also be reported to the international registry at www.lipidregistry.org, although this is now closed.

Lipid emulsion

What is lipid emulsion?

Many types of lipid emulsion are used for this emergency therapy, one example being Intralipid®. Intralipid® (Fresenius Kabi Runcorn, UK) comprises an emulsion of soya oil, glycerol, and egg phospholipids. The efficacy of different ILE therapies in LAST is unknown, but Intralipid is the most widely studied.

History

The lipid resuscitation story began in 1998 when Weinberg and colleagues[18] discovered that Intralipid could resuscitate rats from an LA overdose. This was then tested in dogs, whose response to LA overdose more closely mimics that in humans.[19] I. V. bupivacaine was administered and post-cardiac arrest, the dogs received 10 min of CPR. Subsequently, six dogs received saline and six received Intralipid. All of the dogs in the lipid group had return of spontaneous circulation, whereas all the saline group died.

In February 2006, an editorial in *Anaesthesia* by Picard and Meek disseminated this research. It highlighted that, as with dantrolene, ethical randomized controlled trials of ILE would be impossible. The editorial encouraged the use of ILE in patients with LAST, with publication of the results.[20]

The first two human case reports of ILE use to reverse LA-induced cardiac arrest were published in July[21] and August 2006.[22] In both cases, Intralipid restored cardiac output, allowing full recovery without neurological deficit.

In August 2007, the AAGBI published guidelines recommending that all anaesthetic departments have immediate access to ILE to treat LAST. These guidelines were updated in 2010. In one study, ILE availability in 66 NHS hospitals increased from 21% pre-guidelines (October–December 2006) to 46% at the time of AAGBI guideline publication, to 86% post-guidelines (October 2007–January 2008).[23]

ILE has had an unusual translation from bench to bedside due to its exclusive use in emergencies. In the absence of randomized controlled trials, efficacy has been demonstrated by clinicians willing to try this therapy in a crisis and publish their case reports.[24] It is now an indispensable part of the anaesthetic emergency pharmacopoeia.

Possible mechanisms of action

The precise mechanism of action of ILE remains unclear. Suggested mechanisms include:[25]

(i) The lipid sink hypothesis: This suggests that ILE forms an expanded lipid compartment within the intravascular space, drawing LA off its receptor sites. While easy to understand, this physical explanation may be only partial.

(ii) Enhanced fatty acid metabolism: The heart uses fatty acids as its preferred energy substrate. Bupivacaine inhibits fatty acid oxidation. ILE may provide a source of fatty acids to rescue metabolism. In support of this, experimental inhibition of fatty acid oxidation prevented ILE rescue. Additionally, opening of a channel in the inner mitochondrial membrane, known as the mitochondrial permeability transition pore, has been shown to be a mediator of cell death in the heart. ILE inhibits this pore opening.[26]

(iii) Other: Through *competition*, fatty acids in ILE may directly inhibit LA binding to cardiac sodium channels.[27] Alternatively, ILE can exert a *cytoprotective* effect by activation of Akt (protein kinase B), an enzyme important in cell survival and proliferation. ILE has also been shown to increase intracellular calcium via an *inotropic/ionotropic* mechanism, thus restoring cardiomyocyte function. Another potential mechanism involves altered *pharmacokinetics*, that is, shunting to sequestering organs. A recent study by Litonius and colleagues[28] on eight healthy adult volunteers showed that ILE reduced the context-sensitive half-life of total plasma bupivacaine but exerted no partitioning effect, when low doses of bupivacaine were infused. Finally, ILE exerts a *cardiotonic* effect by a combination of positive inotropy and lusitropy (myocardial relaxation).[29]

Dose

The dosing regimen suggested in the AAGBI guidelines is shown in Figure 1 (http://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf).

Current guidelines suggest two further boluses. The infusion is important, as case reports have described LAST recurring if only the bolus dose has been administered.

Ongoing research

Many questions remain regarding this novel treatment. The optimal dose is unknown. It is also uncertain whether using epinephrine in cardiac arrest, in the presence of ILE, is beneficial or not, although it remains part of the ALS protocol. Another question is whether ILE is associated with long-term sequelae.

Infusion of ILE may also be beneficial in the management of other intoxications, although the evidence base is small.

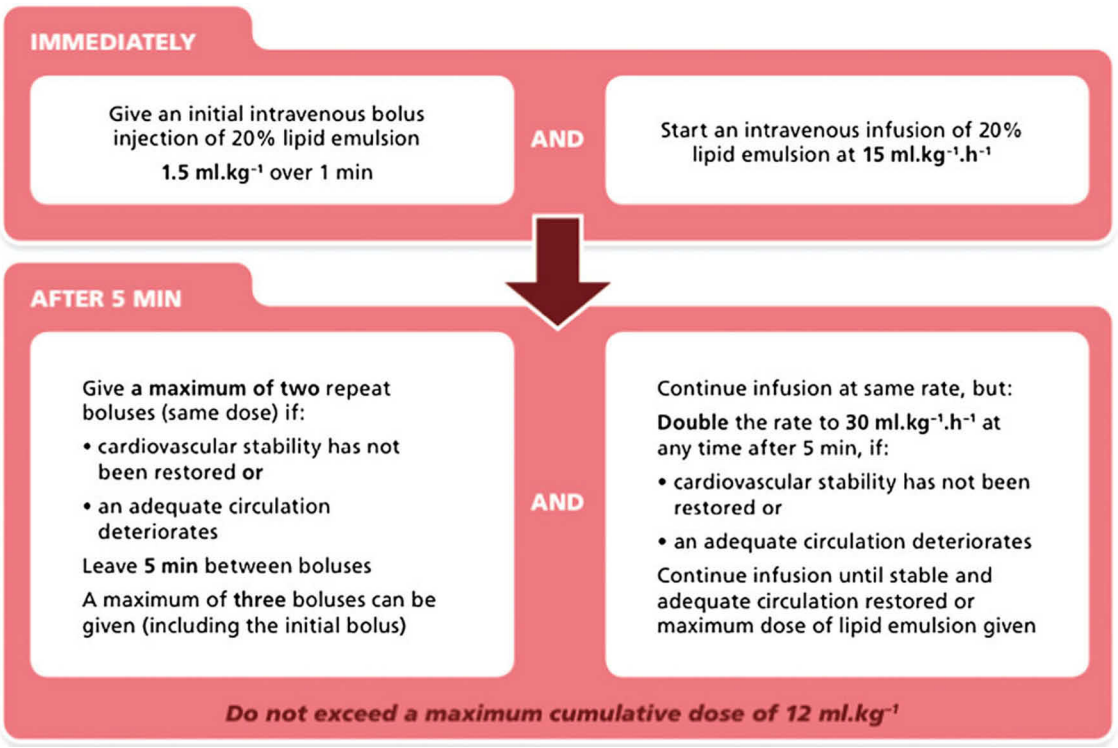

Fig 1 Administration of lipid emulsion therapy from AAGBI guideline on LA toxicity (reproduced with kind permission from the Association of Anaesthetists of Great Britain and Ireland).

Future uses of ILE, which require more extensive research, may include treatment of ischaemia–reperfusion injury. Van de Velde and colleagues[30] demonstrated, in conscious dogs with ischaemia–reperfusion injury, that ILE diminished the associated myocardial stunning. Likewise, ILE administration at the time of reperfusion improves cardiac performance in a rodent model. It may also have a future role in the treatment of pulmonary hypertension.

Conclusion

LAST is rare but may be fatal. While such events are generally unpredictable, many are preventable. As such, clinicians must make every effort to avoid this emergency by taking the precautions described here. If LAST occurs, the key is to recognize it immediately and institute appropriate management. This applies to both anaesthetists and non-anaesthetists. Lipid emulsion therapy has significantly advanced management of this emergency.

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Declaration of interest

G.L.W. holds a US Patent related to lipid resuscitation and is co-founder of ResQ Pharma, LLC.

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