

AAGBI Safety Guidelines

Management of Severe Local Anaesthetic Toxicity

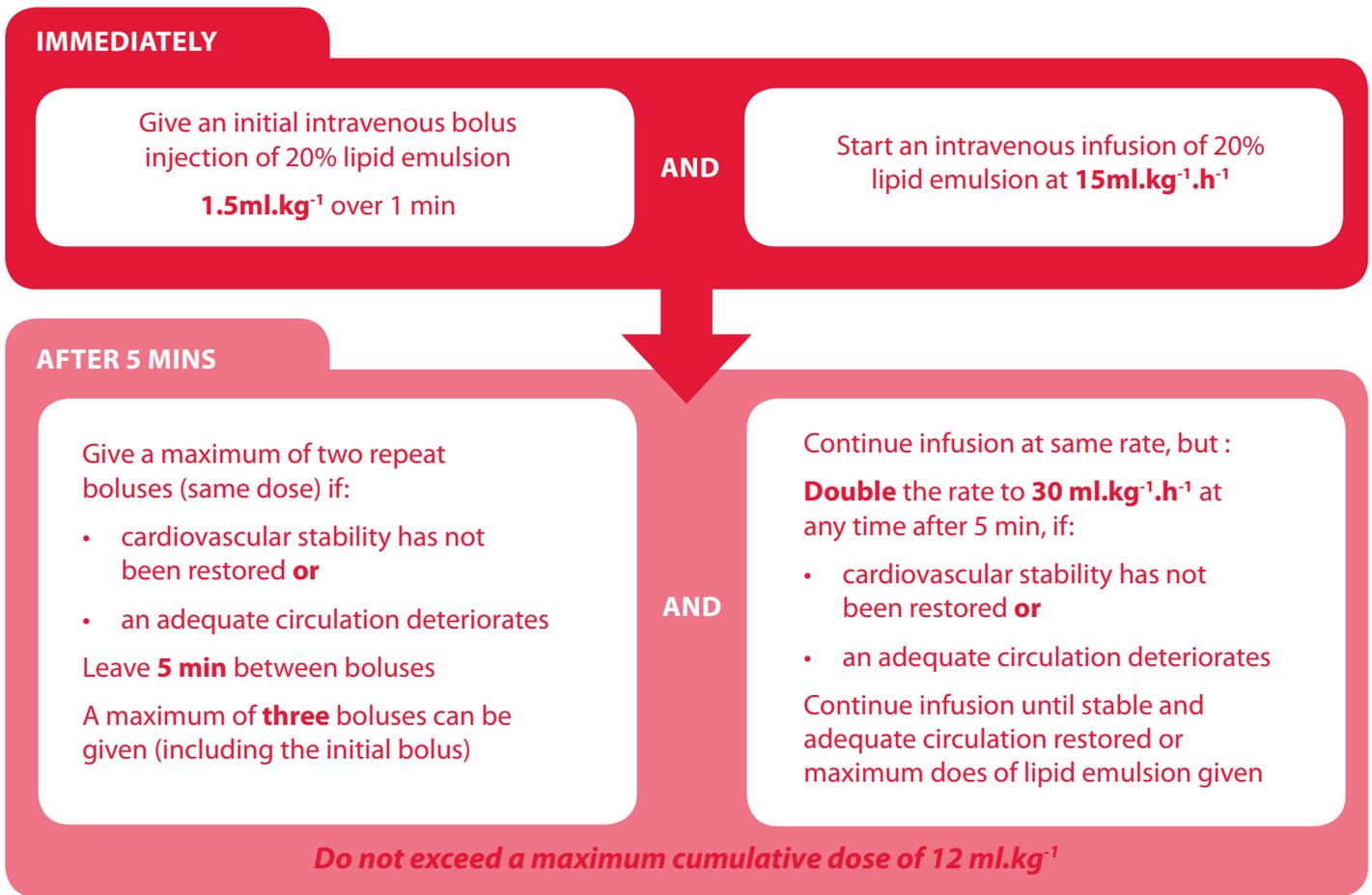


1 Recognition	Signs of severe toxicity: <ul style="list-style-type: none">• Sudden alteration in mental state, severe agitation or loss of consciousness, with or without tonic-clonic convulsions• Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may occur• Local anaesthetic (LA) toxicity may occur some time after an initial injection		
2 Immediate management	<ul style="list-style-type: none">• 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• Consider drawing blood for analysis, but do not delay definitive treatment to do this		
3 Treatment	<table border="0"><tr><td data-bbox="352 853 938 1559">IN CIRCULATORY ARREST<ul style="list-style-type: none">• 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 availableGIVE INTRAVENOUS LIPID EMULSION (following the regimen overleaf)<ul style="list-style-type: none">• Continue CPR throughout treatment with lipid emulsion• Recovery from LA-induced cardiac arrest may take >1h• Propofol is not a suitable substitute for lipid emulsion• Lidocaine should not be used as an anti-arrhythmic therapy</td><td data-bbox="943 853 1533 1559">WITHOUT CIRCULATORY ARREST<p>Use conventional therapist to treat:</p><ul style="list-style-type: none">• hypotension,• bradycardia,• tachyarrhythmiaCONSIDER INTRAVENOUS LIPID EMULSION (following the regimen overleaf)<ul style="list-style-type: none">• Propofol is not suitable substitute for lipid emulsion• Lidocaine should not be used as an anti-arrhythmic therapy</td></tr></table>	IN CIRCULATORY ARREST <ul style="list-style-type: none">• 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) <ul style="list-style-type: none">• Continue CPR throughout treatment with lipid emulsion• Recovery from LA-induced cardiac arrest may take >1h• Propofol is not a suitable substitute for lipid emulsion• Lidocaine should not be used as an anti-arrhythmic therapy	WITHOUT CIRCULATORY ARREST <p>Use conventional therapist to treat:</p> <ul style="list-style-type: none">• hypotension,• bradycardia,• tachyarrhythmia CONSIDER INTRAVENOUS LIPID EMULSION (following the regimen overleaf) <ul style="list-style-type: none">• Propofol is not suitable substitute for lipid emulsion• Lidocaine should not be used as an anti-arrhythmic therapy
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4 Follow-up	<ul style="list-style-type: none">• 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:<ul style="list-style-type: none">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		

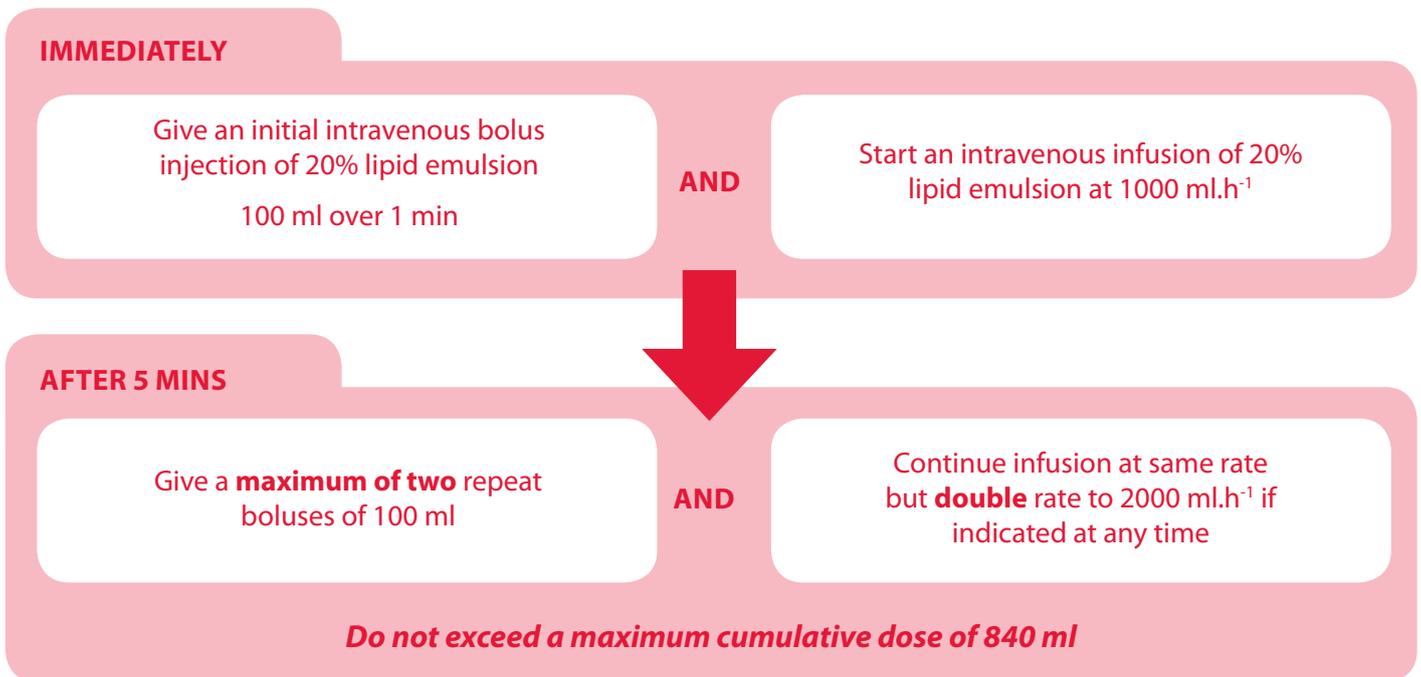
Your nearest bag of Lipid Emulsion is kept

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 light of the clinical data presented and the diagnoses and treatment options available.

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



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 (ANZA).

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Figure 1B. Reproduced by kind permission of the Association of Anaesthetists of Great Britain and Ireland and available for download at: www.aagbi.org/publications/guidelines/docs/la_toxicity_2010.pdf

Management of severe local anesthetic toxicity

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INTRODUCTION

Local anesthetic (LA) agents are widely used, not just by anesthesiologists but by medical staff from all specialties. It is important to be aware of their toxic potential so that any toxic reactions can be detected and treated early. Whilst it is important to be able to treat LA toxicity effectively, it is clearly desirable to avoid LA toxicity whenever possible. For this reason the first section in this article outlines strategies for minimizing the risk of LA toxicity. Knowledge of the properties of local anesthetics as they relate to toxicity will enable the clinician to choose the appropriate technique and local anesthetic for each case.

PROPERTIES OF LOCAL ANESTHETIC AGENTS

Local anaesthetic agents can be classified on the basis of their chemical structure (amides or esters) or their physicochemical properties (short, intermediate or long acting).

Toxic plasma levels of LA can occur following either direct intravascular injection or absorption from the site of injection, resulting in peak plasma levels associated with neurological or cardiovascular symptoms. These plasma level values have been determined for an "average" patient. They need to be individualized for patients with comorbidities or extremes of age.

The amount of systemic absorption depends on the local anesthetic (physicochemical and intrinsic vasoactive properties), site of injection, dose of local anesthetic, addition of vasoconstrictors, and the patient's clinical condition.

Physicochemical properties

Systemic absorption of the more lipid soluble longer acting agents is generally slower. This has implications during continuous administration techniques. The longer acting agents have greater local accumulation while the shorter acting agents have greater systemic absorption.

Intrinsic vasoactive properties

Ropivacaine and levobupivacaine have intrinsic vasoconstrictor properties which may contribute to their longer duration of action and slower systemic absorption. This contributes to a higher safety profile

than racemic bupivacaine, which has an intrinsic vasodilator action.

Site of injection

Independent of the local anesthetic used, systemic absorption increases in the following order:

Sciatic and femoral block < brachial plexus block
< epidural < caudal < intercostal block

Since intercostal blocks are associated with the greatest systemic absorption and hence potentially toxic plasma levels of local anesthetics, it is prudent to use an agent with a good safety profile and consider adding a vasoconstrictor (such as epinephrine). Avoid continuous intercostal blocks unless the patient can be closely monitored.

Dose (concentration and volume) of LA

Increasing the local anesthetic concentration can prolong the duration of the nerve block. However, beyond a ceiling level there is a disproportionate increase in systemic absorption, possibly from saturation of local binding sites and the greater vasodilator effects of more concentrated solutions. This should be kept in mind while selecting the drug concentration. Higher concentrations of local anesthetics do not necessarily translate into longer duration blocks and have a greater potential for systemic toxicity. The recommended maximum single doses for different local anesthetics can be obtained from manufacturer's guidelines (Table 1). This recommendation is not applicable to all patients. As described above, the peak plasma level of a local anesthetic depends on multiple factors. The dose recommendations are only guidelines and should be individualized based on patient factors, type of local anesthetic used and type of block performed.

Addition of vasoconstrictors

When added to the local anesthetic solution, vasoconstrictor agents such as epinephrine could slow systemic absorption and prolong the intensity and duration of action of the nerve block. The extent to which this happens depends on the type and concentration of local anesthetic, and the site of injection. It is more pronounced with the short acting

Summary

An ounce of prevention is worth a pound of cure: Follow the guidelines for prevention of Local Anesthetic toxicity.

Cardiac toxicity from local anesthetics is often irreversible.

Prolonged circulatory arrest can cause brain damage even if resuscitation is successful.

Some authors recommend the use of Intralipid infusion at the first sign of cardiovascular toxicity rather than waiting for cardiac arrest.

Selection of local anesthetic type, concentration and dose must be made on an individual basis after considering patient factors.

Constant vigilance, early detection and treatment are key.

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Table 1. Local anesthetic agents and the recommended maximum dose for infiltration and peripheral nerve blocks, based on a 70kg adult

Local anaesthetic	Recommended maximum single dose
Lidocaine	300mg
Lidocaine with epinephrine	500mg
Prilocaine	600mg
Mepivacaine	400mg
Mepivacaine with epinephrine	500mg
Bupivacaine	225mg
Procaine	1000mg
Chloroprocaine	1000mg

amides (which tend to have a greater systemic absorption), and after intercostal blocks.

The intrinsic vasoactivity of the local anesthetic also modifies the effect of adding epinephrine. Therefore higher concentrations of local anesthetics, which tend to produce vasodilation, benefit more from the addition of epinephrine. However epinephrine has no effect on ropivacaine which has an intrinsic vasoconstrictor property.

Since epinephrine decreases the peak plasma concentration of the local anesthetic after a block, it would seem prudent to add epinephrine to the local anesthetic solution unless contraindicated. The obvious exceptions to this are blocks involving a periphery, such as digital or ankle blocks.

Epinephrine in a 1 in 200 000 concentration added to a local anesthetic solution also serves as a test of intravascular injection. A 5ml solution of 1 in 200000 epinephrine will produce tachycardia, hypertension and changes in T wave amplitude when injected intravascular.

Patient's clinical condition

Patients with liver or kidney disease require a reduction in the dose of local anesthetic because of impaired metabolism and excretion of the LA. Patients with congestive heart failure have decreased volume of distribution and clearance of local anesthetic resulting in higher plasma concentrations. Both acidosis and hypoxemia significantly increase local anesthetic toxicity. Neonates have a 2 to 3 fold prolongation in the elimination half life of amide local anesthetics.

PREVENTION OF LOCAL ANESTHETIC TOXICITY

Patient assessment

Perform a history and physical examination with careful attention to the patient's age and coexisting medical conditions. Ensure that the patient is an appropriate candidate for the regional anesthetic technique and the local anesthetic dose selected.

Choose a local anesthetic agent with the best safety profile and in an appropriate concentration and volume.

Preparation

Ensure availability of:

- Resuscitative equipment and drugs,
- Airway equipment: the means to provide bag mask ventilation, oral and nasal airways, laryngoscopes and endotracheal tubes, laryngeal mask airways.

Obtain consent for the procedure.

Attach standard monitors (ECG, pulse oximetry and non-invasive blood pressure).

Establish intravenous access.

Administer supplemental oxygen.

Consider pre-medication with a benzodiazepine.

Technique

- Choose the appropriate block and determine if the patient really needs a continuous block.
- If the patient needs a continuous block it is prudent to use an intermediate or short acting local anesthetic with less toxic potential. Ensure that the patient remains in a monitored setting until the catheter is removed.
- Check the dose and concentration of local anesthetic and epinephrine prior to performing the block.
- Draw up and label the local anesthetic and keep it with the nerve block equipment away from your anaesthetic drugs.
- While performing the block, aspirate before each injection and discard solution if discolored by blood.
- Inject the total volume in 5ml increments and monitor the patient for signs of toxicity between each injection.

Summary - Physicochemical properties of LA agents and toxicity

- Toxicity from local anesthetics depends on multiple variables and presents in various ways.
- The concept of maximum recommended dose of local anesthetic is not applicable to all patients.
- Cardiac toxicity of local anesthetics is potentiated by acidosis and hypoxemia.
- It is important to individualize the choice of drug, dose and concentration based on the patient's clinical condition and comorbidities.
- **It is also important to remember that toxicity from different local anesthetics is additive.** For example injecting a mixture of two different local anesthetics can produce toxicity even if the doses of the individual local anesthetics are under the recommended maximum dose.

- Maintain verbal contact with the patient during and after the injection.
- When possible perform blocks in mild to moderately sedated patients (i.e. maintaining verbal contact) so that they can report any symptoms of toxicity.
- There is no evidence that nerve blocks cannot be safely performed in patients under general anesthesia. If the patient really requires a block and is uncooperative, it may be safer to perform the block under anesthesia. It is very important in this situation to add epinephrine to the local anesthetic solution to be able to detect intravascular injection. The electrocardiogram should be closely monitored for T wave amplitude changes, which is a more sensitive indicator of intravascular injection in an anesthetized patient than heart rate changes alone.
- Do not leave the patient unattended after a regional anesthetic has been performed.

COMMENTARY ON ALGORITHMS

Box 1 – Recognition of LA toxicity

Recognition of LA toxicity may be difficult, since its mode of presentation is unpredictable and varies between individuals (Figure 2). In addition, presentation may occur at any time in the hour following administration. Onset of toxicity may also be late when LA is infused through a catheter, for example in paravertebral block or peripheral nerve catheters.

Systemic toxicity

Toxic reactions from local anesthetics primarily involve the central nervous system (CNS) or the cardiovascular system (CVS).

CNS toxicity

Symptoms start with lightheadedness, visual and auditory disturbances, perioral numbness and progress to disorientation, shivering, tremors, twitching and ultimately convulsions and coma. There is initial CNS excitation followed by depression. CNS depressant drugs (sedation and general anesthesia) can mask the initial CNS excitation. The potential for CNS toxicity is directly related to local anesthetic potency.

CVS toxicity

Local anesthetics have a direct depressant effect on both the myocardium and the peripheral vascular smooth muscle.

Cardiac effects

Local anesthetics cause a dose dependent prolongation in myocardial conduction which manifests as a prolonged PR interval and QRS duration. In high concentrations LA cause depression of spontaneous pacemaker activity in the SA node resulting in sinus bradycardia and arrest. They also depress the AV node and can cause AV dissociation. They also have negative inotropic effects on the myocardium.

The cardiotoxicity of bupivacaine is unique in that the ratio of the dose required for irreversible cardiovascular collapse (CC) and the dose that will produce CNS toxicity is lower for bupivacaine than other agents. Cardiac resuscitation is more difficult after bupivacaine induced cardiac arrest.

Peripheral vascular effects

With the exception of cocaine, local anesthetics exert a biphasic effect on vascular smooth muscle. They cause vasoconstriction at lower concentrations and vasodilation at higher concentrations. Cocaine produces vasoconstriction at most doses due to its inhibition of norepinephrine reuptake.

Summary

Local anesthetics will cause initial tachycardia and hypertension progressing to bradycardia and a variety of dysrhythmias leading to cardiac arrest.

Local toxicity

Nerve and muscle damage could occur at the site of injection. Skeletal muscle is usually more sensitive to the local irritant properties of local anesthetics than nerve tissue. These reactions are usually reversible.

Side effects of specific LA agents

Methemoglobinemia is seen with large (>600mg) doses of prilocaine. It is clinically insignificant in healthy adults with normal oxygen carrying capacity but can cause hypoxemia in infants.

Cocaine has significant potential for addiction.

Allergic reactions

These are usually more common with esters since they are derivatives of paraaminobenzoic acid which is a well recognised allergen. Allergy to amides though extremely rare can occur. The reactions range from hypersensitivity to anaphylaxis.

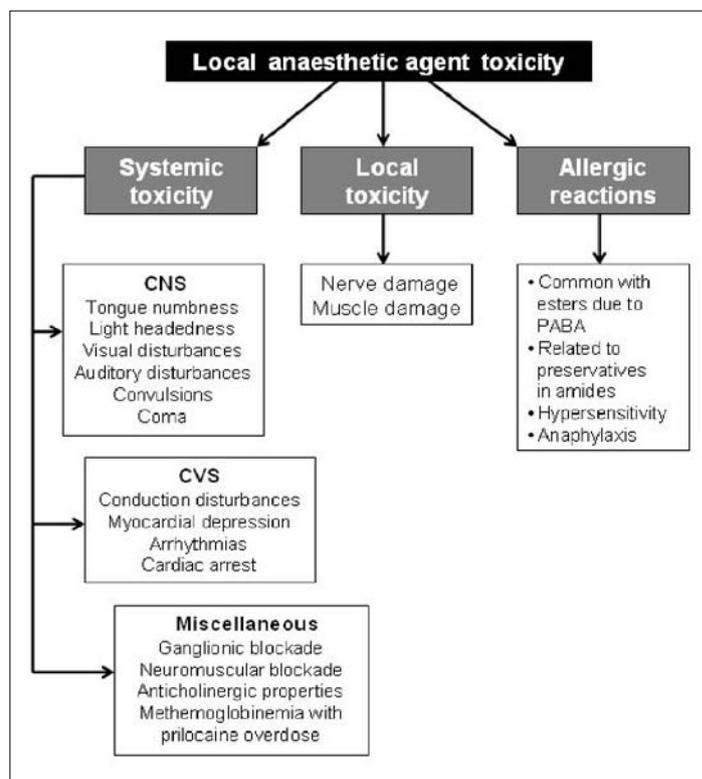


Figure 2. Adverse effects of LA agents

Box 2 - Immediate management

Local anesthetic toxicity from direct intravascular injection is usually immediate and transient. The first step is to stop injecting more local anesthetic. Supportive measures to maintain the airway and treat seizures are usually sufficient. For worsening symptoms or hemodynamic instability proceed to Box 3.

Box 3 - Lipid emulsion infusion for treatment of LA toxicity

- “Intralipid kits” should be available in all locations where local anesthetics are used.²
- The “Intralipid kit” consists of two 500ml bags of Intralipid 20%, infusion tubing, and dosing information.
- Where available, hospital pharmacies carry Intralipid 20%, and so it should be possible to stock it at all locations where local anesthetics are administered and easy to replace when the bags near expiry.
- Intralipid 20% is the formulation that has been used in the majority of the cases to treat cardiac arrest from local anesthetic toxicity. The use of other lipid emulsions is not well documented. Recommended maximum cumulative dose is 12ml.kg⁻¹.
- Although there are many potential side effects of Intralipid infusion the only one likely after acute short term use to reverse local anesthetic toxicity is allergy.²
- It is therefore reasonable to administer Intralipid after conventional therapies have been initiated even in the absence of cardiac arrest.³
- **Propofol is not a substitute to Intralipid 20%** because it is a profound myocardial depressant and because it is formulated in 1% lipid emulsion (rather than 20%).

- There is evidence to suggest that epinephrine in doses greater than 10mcg.kg⁻¹ impairs lipid resuscitation from bupivacaine overdose, possibly by inducing hyperlactatemia.⁴
- In cardiac arrest from local anesthetic overdose, it may be prudent to avoid escalating doses of epinephrine.

CONCLUSIONS

Given the potentially serious consequences of local anesthetic toxicity even if successfully treated, it is prudent to prevent toxicity by following the guidelines for prevention. Early diagnosis of toxic signs and symptoms is important. Most signs of local anesthetic toxicity will respond to supportive measures. For worsening symptoms of toxicity unresponsive to conventional measures, it is reasonable to initiate Intralipid 20% infusion, even in the absence of cardiac arrest.

REFERENCES

1. AAGBI Safety Guide. Management of severe local anaesthetic toxicity (2010). Available at: www.aagbi.org
2. Brull SJ. Lipid Emulsion for the Treatment of Local Anesthetic Toxicity: Patient Safety Implications. *Anesth Analg* 2008; **106**:1337-9.
3. Weinberg GL. Lipid Infusion Therapy: Translation to Clinical practice. *Anesth Analg* 2008; **106**: 1340-2.
4. Hiller DB et al. Epinephrine impairs Lipid Resuscitation from Bupivacaine Overdose: A Threshold Effect. *Anesthesiology* 2009; **111**: 498-505.

FURTHER READING

- Visit www.lipidrescue.org for more information on Intralipid.
- Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine, Fourth edition, Philadelphia, Lippincott, Williams and Wilkins