Lipid rescue: the use of lipid emulsions to treat local anaesthetic toxicity

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ABSTRACT
Despite increasing safety of regional anaesthesia, the growth in the popularity therof implies that local anaesthetic toxicity will occur occasionally. Local anaesthetic cardiotoxicity, even when using "safer" modern local anaesthetics, is notoriously resistant to standard resuscitation. The aim of this paper is to review current knowledge regarding the use of lipid emulsions to treat local anaesthetic toxicity.

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The discovery of lipid rescue: serendipity and science

Weinberg and colleagues proposed and subsequently elucidated the mechanisms behind the use of lipid emulsion as an adjunctive therapy in local anaesthetic cardiotoxicity (Table I).[1-4] The initial animal work was prompted by their observation of severe ventricular dysrhythmias after subcutaneous administration of only 22 mg of bupivacaine to a "carnitine deficient" adolescent.[5] This chance observation prompted investigation of the relationship between bupivacaine toxicity and the underlying metabolic abnormality.[6,7] Weinberg's initial proposal, that lipid pre-treatment would aggravate bupivacaine-induced cardiac arrhythmias, was based on studies indicating that intracellular accumulation of free fatty acid derivatives during myocardial ischaemia contributes significantly to ischaemia-induced arrhythmias.[8,9] However, a series of experiments designed to test this hypothesis indicated that instead of aggravating dysrhythmias, lipid emulsion therapy favourably shifted the dose response curve of bupivacaine-induced asystole. In this rat model, administration of large (15 mg/kg) intravenous dosages of bupivacaine resulted in all lipid-treated animals surviving while all saline-treated controls perished.[1] A subsequent canine study confirmed these favourable results.[3] While all dogs in the control group perished after 10 mg/kg bupivacaine, rapid normalisation of haemodynamic parameters with uniform survival was observed in the lipid-treated animals. The latter study also demonstrated significant improvements in myocardial tissue oxygen tension and pH after lipid treatment.

The findings of this canine study prompted Weinberg to test a novel hypothesis of the mechanism of lipid emulsion in local anaesthetic cardiotoxicity.[9] The hypothesis stated that local anaesthetic-induced cardiotoxicity occurred because of inhibition of the carnitine-dependent processes that transport long-chain

Table I: Mechanisms of cardiotoxicity of local anaesthetic agents

1. **Mechanisms causing cardiac rhythm disturbances, particularly with bupivacaine, include the following**:
   a. Ion channel blockade:
      i. Blockade of sodium channels which inhibits myocardial depolarisation.
      ii. Blockade of the transient outward potassium current (Ito) which inhibits repolarisation of cardiac myocytes.
      iii. Blockade of the voltage-dependent calcium channels, thereby limiting sarcoplasmic calcium release.
      v. Even though both lignocaine and bupivacaine exhibit dose-dependent blockade of the cardiac voltage-gated sodium channels, Clarkson and Hondeghem suggested that the greater cardiotoxicity of the latter is attributed to its strong binding to resting and inactivated sodium channels. Furthermore, local anaesthetic agents bind to and dissociate from sodium channels during systole and diastole respectively. Thus at normal heart rates lignocaine can dissociate completely during diastole, but there is insufficient time for bupivacaine to dissociate from sodium channels. Clinically this often presents as prolongation of the QRS complex and ventricular dysrhythmias and tachycardia.
   b. Depression of conduction in the brainstem area that controls cardiac sympathetic outflow, the nucleus tractus solitarius, leads to hypotension and dysrhythmias.

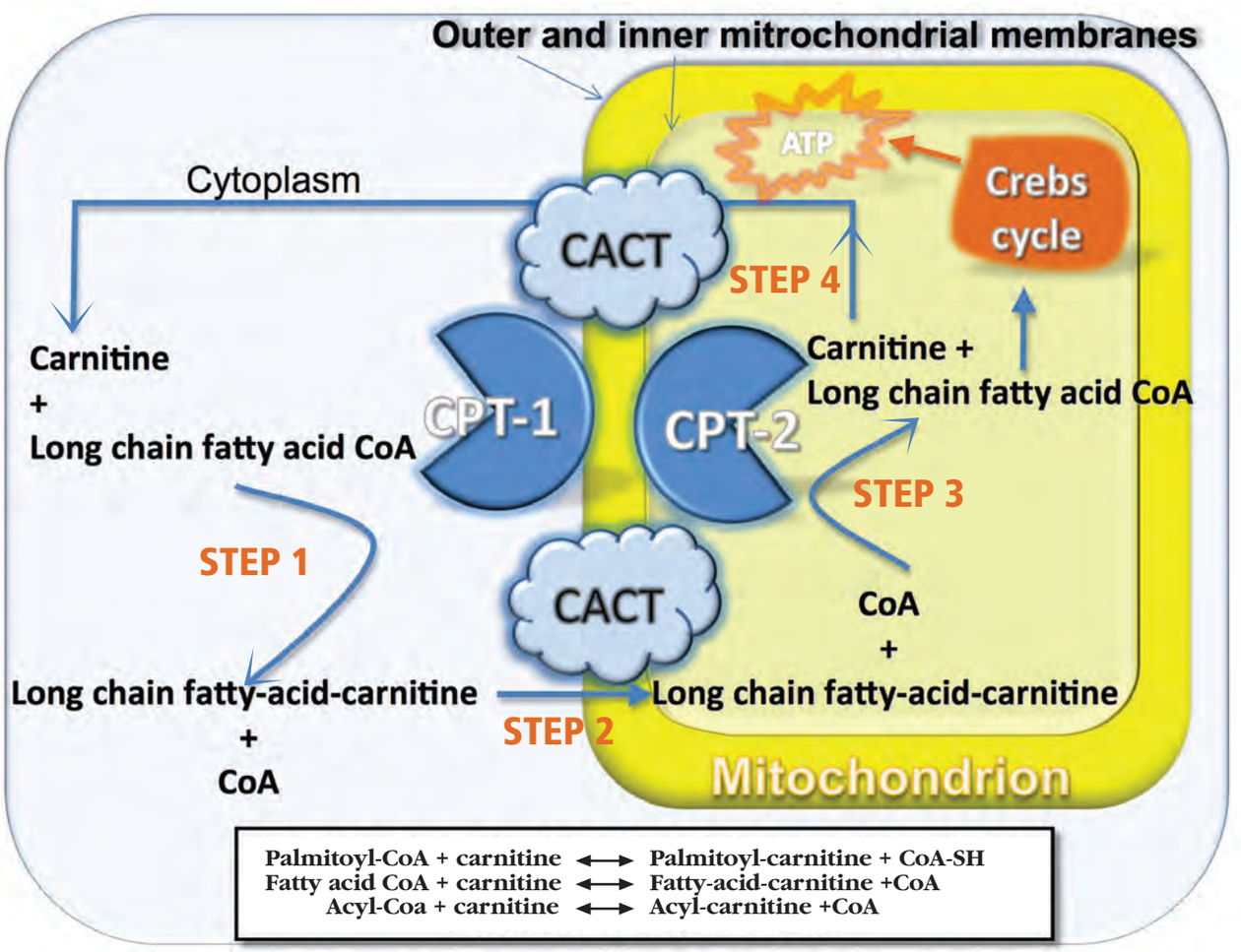
2. **Myocardial depression may result from the following**:
   a. Decreased myocardial calcium release from the sarcoplasmic reticulum and inhibition of calcium excitation-contraction coupling.
   b. Na+/Ca++ exchange pump function is inhibited with decreased cytosolic calcium.
   c. Inhibition of _-adrenergic receptor function.
   d. Inhibition of almost every aspect of oxidative phosphorylation, and complexes 1 and 2 of the electron transfer chain.
   e. Inhibition of nucleus tractus solitarius. (Nonetheless, myocardial depression is not usually pronounced even in severe toxicity.)

3. **A significant cause of hypotension is due to vasodilatation because of both of the following**:
   a. Direct vasodilatation.
   b. Powerful inhibition of peripheral sympathetic reflexes.

(For more detail, see Dippenaar JM. Local anaesthetic toxicity. SAJAA 2007;13(23):92)

free fatty acids into the mitochondrial matrix. This blockade resulted in reduction in the availability of intra-mitochondrial long-chain fatty acids for myocardial oxidative metabolism. Increasing plasma lipid concentrations would, by virtue of mass action, counteract the problematic effects of local anaesthetics on carnitine transport (Figure 1). The Weinberg group could indeed prove their hypothesis that bupivacaine-induced inhibition of carnitine-acylcarnitine translocase and carnitine-dependent mitochondrial long-chain fatty acid transport occurred in isolated mitochondria at clinically relevant toxic concentrations.[9] Furthermore, indirect evidence supporting the validity of this mechanism may be that the potency of inhibition of transport of lipid fuel into mitochondria by local anaesthetics parallels their ability to generate cardiotoxicity.[9]

Figure 1: Carnitine-dependent, long-chain fatty acid transport across the mitochondrial membrane
The carnitine palmitoyltransferase (CPT1 and CPT2) system facilitates specifically long-chain fatty acid entry into subcellular organelles, particularly mitochondria.[86] This mechanism is of particular importance in generating sufficient ATP from fats because only short- and medium-chain fatty acids (length) can enter mitochondria by passive diffusion.



Step 1: Long-chain-specific carnitine acyltransferase (CPT1) activity in the cytosol results in the acyl moiety of acyl-CoA and carnitine being esterified to form acylcarnitine.[87]

Step 2: Carnitine-acylcarnitine translocase (CACT) facilitates transfer of acylcarnitine to the mitochondrion.[86]

Step 3: In the mitochondrion, CPT2 uncouples acylcarnitine. The fatty acids now in the mitochondria are esterified to CoA. Acyl-CoA that is produced is subsequently utilised in fatty acid oxidation in the Krebs/tricarboxylic acid cycle.[10,86]

Step 4: Mitochondrial carnitine released in step 3 is transferred back into the cytosol by CACT. Bupivacaine and other local anaesthetic agent toxicity block the carnitine transporter system, thereby limiting the entry of long-chain fatty acids into the mitochondrion. In the heart, as opposed to other organs, more than 80 to 90% of normal aerobic cardiac metabolism results from fatty acid oxidation, ketones and lactate.[1,28,90] The disproportionate cardiotoxicity relative to the neurotoxicity of bupivacaine can be related to cardiac preference for lipid compared to the brain's preference for carbohydrates as fuel sources.[32] It may also explain why bupivacaine and other local anaesthetic cardiotoxicity is so very resistant to therapy.[1]

Weinberg's canine experiments elicited upbeat editorial comment. Groban and Butterworth questioned whether lipid emulsion therapy indeed represented a "silver bullet" for treating bupivacaine cardiotoxicity.[10] They proposed that lipid emulsion be employed in human bupivacaine intoxication only "after other, more conventional treatments had proven unsatisfactory" as these observations in animals, albeit striking, were yet to be confirmed.[10]

The first human case describing resuscitation from local anaesthetic-induced cardiotoxicity facilitated by lipid emulsion was reported by Rosenblatt and colleagues almost a decade after Weinberg's initial report.[11] This case describes asystole with paroxysms of ventricular tachycardia after 100 mg bupivacaine and 300 mg mepivacaine had been administered as an interscalene brachial plexus block. The arrhythmias were refractory to multiple drug therapy and counter shocks. After 30 minutes of unsuccessful resuscitation, as a last resort before initiating cardiopulmonary bypass, 100 ml of 20% Intralipid® was administered intravenously. Within seconds of completion of the lipid emulsion bolus, return of spontaneous circulation and a normal blood pressure occurred. The patient survived without neurological deficit.

The salient features of other published case reports are outlined in Table II. All case reports describe rapid recovery when lipid emulsion therapy was employed to facilitate resuscitation following local anaesthetic-induced cardiotoxicity. The case reports indicate efficacy of lipid emulsion therapy with the majority of amide local anaesthetics currently in clinical use, including bupivacaine, mepivacaine, ropivacaine, levobupivacaine and lignocaine. It is interesting to note that despite the benign reputation[1] of ropivacaine,[2–16] the case reports include references to ropivacaine-induced cardiotoxicity,[17,18] Other insights gained by studying these cases are that although Intralipid® is the most commonly used agent other lipid emulsions (Medialipid® and Liposyn®) have also been employed successfully for lipid rescue. Furthermore, the first patients[11,19] rescued with the help of lipid emulsions had severe concomitant disease (ischaemic heart disease, advanced age, pulmonary disease, end-stage renal disease). It is not surprising that regional anaesthesia was employed in these patients.[20-22]

Mechanisms of lipid rescue

Two theories, namely the lipid sink and lipid flux theories, dominate the current understanding of the mechanisms of lipid rescue.

The lipid sink theory[1,2,19,23] hypothesises that highly lipophilic drugs sequestrate into the "newly created intravascular lipid compartment".[24] This theory originated from early rat experiments in which myocardial bupivacaine concentrations decreased rapidly after lipid rescue.[1] Later work confirmed more rapid clearance of bupivacaine from rat myocardium when lipid emulsion therapy was compared to control. Support for this theory also comes from a lipid-aqueous ratio of bupivacaine in an Intralipid®-plasma mixture of 11.9 to 1[1] and the ability of lipid emulsions to terminate convulsions. If the lipid sink hypothesis holds true, serum local anaesthetic concentrations should increase after lipid rescue. This was not borne out by the second case described by Litz, where a decrease in bupivacaine concentrations was observed after lipid rescue.[25]

The lipid flux theory is based on the powerful ability of local anaesthetics to inhibit the carnitine transporter system, the enzyme system responsible for transfer of long-chain fatty acids into the mitochondrial matrix for β-oxidation.[4,9,26,27] Administration of lipid emulsion provides medium- and short-chain fatty acids to supply the mitochondria with sufficient substrate.[26,28] Weinberg suggests that restoring the heart's preferred fuel supply (fatty acids) could explain why resuscitation is so rapid following lipid emulsion.[28]

There is collateral evidence supporting the lipid flux hypothesis. Firstly, in an isolated rat heart model of bupivacaine cardiotoxicity, Stehr and colleagues demonstrated improved myocardial contractility at plasma concentrations of lipid far lower than that needed to provide a lipid sink effect.[29] Secondly, the promotion of substrate influx into cells that follow administration of insulin (2 IU/kg) combined with glucose and potassium invokes mechanisms that parallel that of the lipid flux theory.[30,31]

Insulin and reversal of local anaesthetic-induced cardiotoxicity

The hypothesis that insulin, glucose and potassium infusion can be a useful adjunct in resuscitation from bupivacaine cardiotoxicity has been confirmed in two animal studies.[30,31] Because the dosage of insulin employed was 2 IU/kg, anaesthesiologists have been extremely hesitant to translate this research into clinical practice.[28]

The beneficial effects of insulin in the presence of local anaesthetic cardiotoxicity include promotion of the transient outward potassium current, intracellular potassium movement – which causes hypokalaemia – and an increase in the rate of depolarisation of the slope of phase zero (Vmax) of the cardiac action potential. Insulin will also facilitate sarcoplasmic calcium transport because of calcium adenosine triphosphatase activation. The first two mechanisms have antiarrhythmic actions while the increased calcium flux helps counteract deleterious effects of local anaesthetics on myocardial contractility. However, Weinberg and VadeBoncouer suggested that insulin and lipid act via similar mechanisms in local anaesthetic cardiotoxicity. The increase in glycolysis and glucose oxidation that follows insulin administration may be the driver that provides sufficient substrate for oxidative phosphorylation and adenosine triphosphate (ATP) production.[28,32]

The availability of lipid emulsion and preparedness to use it

In 2006, Corcoran and colleagues surveyed the preparedness of 135 academic anaesthesiology departments in the USA to employ lipid rescue. Seventy-four per cent of the departments reported they would *not* consider using lipid emulsion therapy for local anaesthetic cardiotoxicity.[33] However, only one year after the first case report, Williamson and Haines reported that three-quarters of labour wards in the United Kingdom already had lipid emulsion available or planned to stock it.[34] The difference between these studies may well be that the first study was performed before publication of the first successful human lipid rescue. The UK study also questioned why lipid emulsion was not available. The three main reasons cited for the unavailability of lipid emulsion were that the evidence base was not strong enough to justify clinical use, that lipid was not considered necessary, and that anaesthesiologists were unaware of the research regarding lipid rescue.[34] While the first reason may be debated, the last two points are disconcerting and represent a significant reason for the publication of review articles on this topic.

Picard and Meek point to parallels between the anaesthesia community's initial reluctance[33-35] to embrace lipid rescue and the slow initial clinical acceptance of dantrolene for treatment of malignant hyperthermia. Because of the rarity and severity of local anaesthetic-induced cardiotoxicity, it is not possible or ethical to conduct human research on the underlying problem.[36] Human case reports[11,19,20,37-45] describing successful lipid rescue are therefore invaluable.[26]

When should lipid therapy be started?

The initial recommendations stated that lipid rescue be employed "only after other, more conventional treatments have proven unsatisfactory"[10] or that it "should be considered before ceasing resuscitative efforts even if its use is contemplated after a significant delay in the setting of prolonged cardiac arrest".[46] As confidence with this therapeutic modality grows, case reports indicate progressively earlier administration of lipid emulsion during resuscitation.[19-22,37,38] This has led Weinberg to retract his earlier conservative recommendation "that lipid infusion be delayed until standard resuscitative measures failed".[10,23,46,47]

What are the implications of earlier institution of lipid therapy in the presence of local anaesthetic toxicity? Should lipid

Table II: Published cases in which lipid rescue has been employed*

Case	Local anaesthetic	Time to first symptoms after local anaesthesia injection	Presenting feature	Cardiac arrest, electrical or conduction changes?	Timing of lipid administration	Total duration of CPR before ROSC†	Dose of lipid	Comments
11) Marwick et al. 2009	Bupivacaine	Immediate	Convulsions	Ventricular fibrillation	Within first minute of asystole	5 minutes	Bolus: 150 ml Intralipid 20% over 1 minute Infusion: Intralipid 350 ml 20% over 40 minutes	Recurrence of cardiotoxicity
10) Smith et al. 2008	Bupivacaine 155 mg with epinephrine 1:400 000 and clonidine 100 µg (sciatic nerve block)	Immediate	Loss of consciousness and tonic-clonic seizure	Asystole	Within first minute of asystole	5 minutes	Bolus: 250 ml Intralipid 20% over 2 minutes Infusion: Intralipid 20% 15 ml/min, duration not stated	Patient awake and responsive by 90 minutes
9) Warren et al. 2008	Mepivacaine 450 mg plus bupivacaine 50 mg (supraclavicular brachial plexus block)	5 minutes	Laboured breathing, apnoea, unresponsiveness	Ventricular fibrillation, Torsades des pointes	Infusion started 10 minutes after CPR commenced	25 minutes	Liposyn III 20%. No bolus administered, 250 ml infused over 30 minutes	The omission of a bolus probably resulted in delayed lipid effect 26 defibrillations Survived intact
8) Litz et al. 2008	Mepivacaine 300 mg (infraclavicular) augmented 15 minutes later by prilocaine 100 mg (axillary block)	Within 5 minutes of second injection	Dizziness, nausea, agitation	Heart rate increase from 76 to 92, supraventricular extrasystoles, paroxysms of ventricular bigeminus	Not specified	Not applicable	Intralipid® 20%. Bolus 50 ml repeated after 3 minutes. Infusion 0.25 ml/kg/hr of a further 100 ml.	Regained consciousness within 5 minutes of starting Intralipid® Extrasystoles gone after approximately 200 ml (10 minutes) of Intralipid® infused
7) Ludot et al. 2008	Lignocaine 110 mg plus ropivacaine 82.5 mg (lumbar plexus block)	15 minutes	Ventricular tachycardia	Ventricular tachycardia	Not specified	Not applicable. Rhythm recovered 2 minutes after starting lipid	Medialipid 20% 150 ml over 3 minutes	Patient under general anaesthesia while block administered
6) McCutchen et al. 2008	Ropivacaine 150 mg (femoral nerve block) plus bupivacaine 150 mg (sciatic nerve block)	20 seconds	Convulsions	Ventricular tachycardia with pulse and respiratory effort	3 minutes after second convulsion	No CPR administered Reversion to sinus rhythm after Intralipid® bolus	100 ml 20% Intralipid® bolus over 60 seconds followed by 400 ml over 15 minutes	Possible overdose of local anaesthetic agents Mental state normal in 2 hours
5) Spence 2007	Lignocaine 80 mg plus bupivacaine 65 mg (epidural analgesia during labour)	90 seconds after last bolus	Restlessness, agitation, twitching	No report of any ECG or circulatory changes	Not specified	Not applicable. Fully conscious within 30 seconds of administration	100 ml 20% Intralipid® as a bolus followed by 400 ml Intralipid® over unspecified period	Letter to the editor Intravascular catheter "migration" and blood able to be subsequently aspirated from catheter
4) Zimmer et al. 2007	Bupivacaine 15 mg bolus followed 20 minutes later by 28 mg fractionated over 15 minute period (epidural anaesthesia)	15–20 minutes after last bupivacaine bolus	Shivering, central nervous system excitation	No cardiac arrest, supraventricular tachycardia, ventricular extrasystoles	45 minutes after last bupivacaine bolus	Not applicable	100 ml 20% Lipofundin® followed by infusion 0.5 ml/kg/hr	Blood in epidural catheter after aspiration
3) Foxall et al. 2007	Levobupivacaine 100 mg (lumbar plexus block)	Seconds	Unresponsiveness and convulsions	No cardiac arrest, reduced QRS voltage and broadening of QRS complexes	4 minutes after administration of block	Not applicable. "Rapid normalisation" of QRS morphology with infusion	100 ml Intralipid® over 5 minutes	Patient survived without sequelae
2) Litz et al. 2006	Ropivacaine 400 mg (axillary plexus block)	15 minutes	Dizziness, drowsiness, loss of consciousness, convulsions	Ventricular extra systoles, bradycardia, asystole	After 10 minutes CPR	20 minutes	100 ml of 20% solution Intralipid® as a bolus followed by infusion of 10 ml per minute	Return of electrical activity (initially broad complex tachyarrhythmia) after 200 ml Intralipid®. Patient survived without sequelae
1) Rosenblatt et al. 2006	Bupivacaine 100 mg plus mepivacaine 300 mg (interscalene brachial plexus block)	30 seconds	Incoherence and convulsions	Asystole	After 20 minutes CPR	20 minutes	100 ml of 20% solution of Intralipid® as a bolus followed by 0.5 ml/kg/minute for 2 hours (about 4900 ml in total)	Sinus rhythm restored very quickly (15 seconds) after administration of bolus. Patient survived without sequelae

* All information is extracted as accurately as possible from published case reports
† All ROSC: return of spontaneous circulation

emulsion be administered only after the occurrence of cardiotoxicity, only after cardiac arrest or only after failed resuscitation occurs? Another pertinent question is whether lipid should be administered immediately after local anaesthetic-related neurotoxicity? Convulsions secondary to local anaesthetic toxicity are usually easily managed and, in isolation, are probably not strong indications for use of lipid rescue. However, it is well described that bupivacaine-induced cardiotoxicity occurs in closer relationship to neurological signs than is the case with other local anaesthetic agents.[12,18] The recommendations for commencement of lipid emulsion therapy by Weinberg (Figure 2)[8] and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) (Figure 3)[49] are as follows:

1. Commence therapy at the first signs of local anaesthetic-induced cardiotoxicity. Preferably administer the lipid while a spontaneous circulation is still present.
2. We and others[23,48] further argue that bupivacaine-induced neurotoxicity may well be an indication to administer lipid emulsion.

Protocol for therapy

As yet, no standard protocol for lipid emulsion therapy exists.[8] In the presence of local anaesthetic toxicity, both AAGBI[49] and Weinberg, on the lipid rescue website,[8] currently recommend administration of an initial bolus of 1.5 ml/kg of 20% lipid emulsion over one minute. The bolus may be repeated twice at five-minute intervals if an adequate circulation has not been restored[49] or if asystole persists.[8]

Both aforementioned sources recommend following the bolus with an infusion of 20% lipid emulsion at 0.25 ml/kg/minute. While AAGBI and Weinberg both recommend continuing the infusion, the former recommends doing this over a 20-minute period (i.e. finishing the rest of the 500 ml bag over this time) while the latter recommends the infusion be continued for 30 to 60 minutes. The infusion rate may be increased to 0.5 ml/kg/minute should an adequate circulation not be restored. Notwithstanding the nuances of a particular dosing regimen, the lipid infusion should be continued until a stable and adequate circulation has been restored.[8,49]

Practitioners are frequently uncertain of the dose of lipid emulsion to be administered during resuscitation.[50] To prevent such uncertainty, both Weinberg[8] and the AAGBI[49] have recommended that dosing instructions should be attached to the stock of lipid held for treating local anaesthetic toxicity.

Reoccurrence of toxicity

Following inadvertent bupivacaine intoxication, we experienced a case of reoccurrence of cardiotoxicity 40 minutes after administration of the last of the Intralipid®.[50] Reoccurrence of toxicity may have many causes. Serum concentrations of lipid may decrease due to redistribution and metabolism. The already long elimination half life of intravenously administered bupivacaine (3.5 hours)[51] may be prolonged further by impaired hepatic perfusion and dysfunction.

Safety considerations regarding lipid emulsion administration

Lipid emulsions used for total parental nutrition are commonly 20% soybean oil emulsions[52] that are classified according to droplet size. Micro-, mini- and macro-emulsions have mean droplet sizes less than 0.1 μm, less than 1 μm and greater than 1 μm respectively. The mini-emulsion is the most commonly used soybean oil formulation for total parental nutrition. Soybean emulsions are stabilised by addition of emulsifiers (typically egg phospholipids) that possess hydrophobic and hydrophilic heads that coat the submicron droplet. Three physicochemical factors, namely pH, free fatty acid concentration and globule size, influence the stability of lipid emulsions. Progressive degeneration of long-chain triglycerides to free fatty acids results in a pH of 9 immediately after manufacturing, decreasing to a pH of 6 toward the end of the 24-month shelf life. Decreases in pH reduce phospholipids' anionic electrostatic charge, causing

Figure 2: Weinberg website lipid rescue protocol

LipidRescue™

TREATMENT FOR LOCAL ANESTHETIC-INDUCED CARDIAC ARREST

PLEASE KEEP THIS PROTOCOL ATTACHED TO THE INTRALIPID BAG

In the event of local anesthetic-induced cardiac arrest that is unresponsive to standard therapy, in addition to standard cardio-pulmonary resuscitation, Intralipid 20% should be given i.v. in the following dose regime:

- **Intralipid 20% 1.5 mL/kg over 1 minute**
- **Follow immediately with an infusion at a rate of 0.25 mL/kg/min,**
- **Continue chest compressions (lipid must circulate)**
- **Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation is restored**
- **Continue infusion until hemodynamic stability is restored. Increase the rate to 0.5 mL/kg/min if BP declines**
- **A maximum total dose of 8 mL/kg is recommended**

In practice, in resuscitating an adult weighing 70kg:

- ***Take a 500ml bag of Intralipid 20% and a 50ml syringe.***
- ***Draw up 50ml and give stat i.v., X2***
- ***Then attach the Intralipid bag to an iv administration set (macrodrip) and run it .i.v over the next 15 minutes***
- ***Repeat the initial bolus up to twice more – if spontaneous circulation has not returned.***

If you use Intralipid to treat a case of local anaesthetic toxicity, please report it at www.lipidrescue.org. Remember to restock the lipid. Ver 7/06

emulsion instability and promoting lipid droplet coalescence. Lipid droplets smaller than one micron in diameter are metabolised by lipoprotein lipase located in the vascular endothelium. Larger globules that form in unstable infusions are phagocytised by macrophages of the reticuloendothelial system. The phagocytosis process produces reactive oxygen species, the liver being the principal organ injured in this process.[52] Shortly after commencement of infusion of an unstable lipid emulsion, a pyrogenic response typified by fever, chest pain and signs of an anaphylactic-type reaction can manifest. This type of reaction is rare nowadays due to improved manufacturing processes. Subacute reactions resulting from microvascular obstruction present as hepatic dysfunction two to three days later. If the globules exceed 5 μm in diameter, splenic, cerebral or pulmonary emboli and pulmonary hypertension can occur.[53]

Even rapid administration of large doses of stable lipid emulsion can have potential side-effects, which may be aggravated by the presence of high plasma levels of local anaesthetic agents. Local anaesthetics induce myocardial depression, even at levels found in normal clinical use.[14,16,18] Myocardial depression will be aggravated by increases in both right[53] and left ventricular afterload that are associated with both lipid emulsion therapy and local anaesthetic toxicity. Local anaesthetic toxicity increases centrally mediated sympathetic nervous system outflow, thereby increasing left ventricular afterload.[29,54] Lipid emulsion may induce vasoconstriction secondary to inhibition of nitric oxide

THE ASSOCIATION OF ANAESTHETISTS
of Great Britain & Ireland

Guidelines for the Management of Severe Local Anaesthetic Toxicity

Signs of severe toxicity:
- Sudden loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
- Local anaesthetic (LA) toxicity may occur some time after the initial injection

Immediate management:
- 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 pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Assess cardiovascular status throughout

Management of cardiac arrest associated with LA injection:
- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that they may be very refractory to treatment
- Prolonged resuscitation may be necessary; it may be appropriate to consider other options:
  - o **Consider the use of cardiopulmonary bypass if available**
  - o **Consider treatment with lipid emulsion**

Treatment of cardiac arrest with lipid emulsion: (approximate doses are given in red for a 70-kg patient)
- Give an intravenous bolus injection of Intralipid® 20% 1.5 ml.kg^{-1} over 1 min
  - o Give a bolus of 100 ml
- Continue CPR
- Start an intravenous infusion of Intralipid® 20% at 0.25 ml.kg^{-1}.min^{-1}
  - o Give at a rate of 400 ml over 20 min
- Repeat the bolus injection twice at 5 min intervals if an adequate circulation has not been restored
  - o Give two further boluses of 100 ml at 5 min intervals
- After another 5 min, increase the rate to 0.5 ml.kg^{-1}.min^{-1} if an adequate circulation has not been restored
  - o Give at a rate of 400 ml over 10 min
- Continue infusion until a stable and adequate circulation has been restored

Remember:
- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1 h
- Propofol is not a suitable substitute for Intralipid®
- Replace your supply of Intralipid® 20% after use

Follow-up action:
- Report cases from the United Kingdom to the National Patient Safety Agency (via www.npsa.nhs.uk). Cases from the Republic of Ireland should be reported to the Irish Medicines Board. Whether or not lipid emulsion is administered, please also report cases to the LipidRescue™ site: www.lipidrescue.org.
- If possible, take blood samples into a plain tube and a heparinised tube before and after lipid emulsion administration and at 1 h intervals afterwards. Ask your laboratory to measure LA and triglyceride levels (these have not yet been reported in a human case of LA intoxication treated with lipid).
- Please read the notes overleaf

Your nearest bag of Intralipid® is kept .....

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Notes
- Intralipid® 20% has been shown to reverse LA-induced cardiac arrest in animal models [1,2] and in human case reports [3,4], and its use has been reported in the treatment of life-threatening toxicity without cardiac arrest [5]. Its therapeutic potential has been highlighted by the National Patient Safety Agency [6].
- Intralipid® 20% 1000 ml should be immediately available in all areas where potentially cardiotoxic doses of local anaesthetics are given, along with guidelines for its use.
- In the UK, Intralipid® is distributed by Fresenius Kabi Ltd. It is distributed in the Republic of Ireland by Cahill May Roberts.
- Intralipid® is readily available from most hospital pharmacies, which may also be able to help departments with timely replacement of bags nearing expiry.
- The usefulness of other lipid emulsions is not known, as published work to date has only used Intralipid®.
- Although some propofol preparations are provided in Intralipid®, e.g. Diprivan®, these are not a suitable alternative, due to the significant cardiovascular depression caused by the propofol. This does not preclude the use of small, incremental doses of propofol to control seizures.
- The use of Intralipid® in this way is relatively novel. Therefore, future laboratory and clinical experiences are likely to dictate further refinement of the method.
- This guideline document will be reviewed regularly and updated when necessary. Updated versions will be available on http://www.aagbi.org and http://www.lipidrescue.org.
- Further educational matter is available at http://www.lipidrescue.org.

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

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Available online at:
http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf.
(Currently being reviewed)

Figure 3: AAGBI lipid rescue protocol

production[55,56] and/or due to direct increases in central sympathetic nervous system activity. A recent case report observed an increase in serum amylase after lipid rescue, a possible indication of pancreatic injury.[50] However, no other complications of lipid emulsion therapy after local anaesthetic toxicity have been reported yet. None of the aforementioned potential complications, with the possible exception of known allergy, should deter lipid administration in the presence of local anaesthetic-induced cardiac arrest.[47]

Lipid emulsions infused as part of total parenteral nutrition can also produce adverse reactions. These include aggravation of hypoxia due to impairment of hypoxic pulmonary vasoconstriction[58] and oxygen diffusion capacity[59] and increasing tissue oxygen consumption.[60] In addition, allergic reactions, thrombophlebitis, muscle weakness, seizures in children, increased intracranial pressure after traumatic head injury, warfarin resistance (because lipids facilitate the anticoagulant binding to albumin), and impaired immune, reticuloendothelial and inflammatory responses have all been reported.[47,52]

Availability of lipid emulsions in southern Africa

Intralipid® (Fresenius Kabi, South Africa) is available as a 20% solution and is packaged in 100 ml and 500 ml bags. It has a shelf life of 18 months from the date of manufacture.

The use of propofol for lipid rescue

Propofol has been touted as a source of lipid in local anaesthetic toxicity. Propofol is poorly water soluble and is dissolved in the same emulsion used for lipid rescue and total parenteral nutrition.[61] However, to deliver adequate doses of lipid will require administration of half to one litre of 1% propofol.[61] The accompanying huge propofol dose will undoubtedly result in severe haemodynamic side effects due to vasodilatation and myocardial depression.[63] Propofol interferes with mitochondrial functioning by inhibiting carnitine palmitoyltransferase-1[63,64] and inhibiting electron transport by causing failure of the respiratory chain at complex II.[63] The use of propofol to manage patients with local anaesthetic toxicity (either for sedation, termination of convulsions, or as a source of lipid) may aggravate local anaesthetic cardiotoxicity and is considered to be contraindicated.[65]

CPR, vasopressors and local anaesthetic (bupivacaine) cardiotoxicity

Weinberg and colleagues' early animal experiments demonstrated the superiority of lipid in reducing the toxic dose of bupivacaine and in effecting resuscitation over saline controls. These studies did not employ adrenaline as part of their resuscitation protocols.[1,3,26] However, current American Heart Association Advanced Cardiac Life Support protocol advocates the use of adrenaline during CPR.[46] These conflicting approaches have initiated research regarding the relevant role of lipid in resuscitation. The main question currently is whether lipid emulsion should be used alone or be combined with vasopressin ± adrenaline during local anaesthetic-induced cardiac arrest.[66] Currently, four pertinent schools of thought exist:

1. **Use of low-dose adrenaline alone is effective to treat local anaesthetic (bupivacaine) toxicity**. In an instructive letter to the editor, Moore[67] argued that aggressive maintenance of the circulation by treatment of bradycardia with small (300 μg to 500 μg) intravenous boluses of epinephrine and the early institution of CPR solves most cases of bupivacaine-related cardiotoxicity, without requiring recourse to lipid emulsion therapy.[68,69] This approach has support from animal experiments.[70,71]

2. **Use of lipid rescue is effective and superior to vasopressor therapy in local anaesthetic toxicity**. Weinberg and colleagues[4] and Di Gregorio and colleagues[66] demonstrated the superiority of lipid emulsion therapy over epinephrine in bupivacaine-induced cardiotoxicity in rat models. The reasons elucidated for achieving better results with lipid were superior cardiac and metabolic function during and after resuscitation,[4] and adrenaline-induced aggravation of bupivacaine-related dysrhythmias.[4,15,72,73] However, rats treated with adrenaline showed a decline in haemodynamics after 10 minutes.

3. **Lipid rescue is effective, but exceeding particular doses of adrenaline impedes the effectiveness of resuscitation**. Recent investigations described a threshold effect of adrenaline on survival in local anaesthetic toxicity and lipid rescue. When doses exceeding 10 μg/kg were administered, adrenaline impaired long-term success of lipid resuscitation after bupivacaine intoxication. Hicks and colleagues' study,[74] discussed below, may also be relevant here. The reasons suggested for the poor outcome with higher dosages of adrenaline include the development of pulmonary oedema, lactic acidosis and increased myocardial work.

4. **Lipid rescue is not superior to the use of vasopressor in local anaesthetic systemic toxicity**. Mayr and colleagues observed that vasopressin or adrenaline or a combination of the two was successful while lipid emulsion alone was uniformly unsuccessful in effecting resuscitation in a porcine model of bupivacaine cardiotoxicity.[71] The explanation offered for the divergent successes of lipid versus vasopressor therapy focussed on study design. Mayr and colleagues introduced a period of apnoea after bupivacaine administration while in the Weinberg and Di Gregorio[66] studies hypoxia and delay in resuscitation were avoided. Hicks and colleagues employed a swine model of bupivacaine-induced cardiac arrest in which a high dose of adrenaline (100 μg/kg) was administered and a one-minute period of apnoea was allowed before resuscitation commenced. Lipid emulsion did not improve the rate of return of spontaneous circulation when added to epinephrine and vasopressin.

What clinically relevant conclusions can be drawn from these divergent results? Cave and Harvey commented that lipid emulsion therapy is superior to vasopressor therapy, despite the results of Mayr's and Hick's studies being confounded by asphyxiation.[75] Weinberg still advocates following the American Heart Association Advanced Cardiac Life Support protocol advocating the use of adrenaline.[46] Whether the findings of rodent studies will result in adrenaline dose modification during CPR in humans, or only during lipid emulsion therapy, is at present not clear.[76] It is interesting that investigations into the place of vasopressor use in lipid rescue from local anaesthetic toxicity may have wider ramifications in terms of current resuscitation practices.[77] We believe that the American Heart Association Advanced Cardiac Life Support protocol should specify that local anaesthetic cardiotoxicity is an indication for lipid emulsion therapy.

The use of lipid emulsions to reverse toxicity of other drugs

Lipid emulsion therapy reliably reverses cardiotoxicity caused by a variety of lipophilic drugs, including tricyclic antidepressants, calcium channel blockers, propranolol and thiopentone.[24,25,66,78] Case reports have been published on successful lipid rescue following cardiotoxicity involving haloperidol,[79] bupropion and lamotrigine.[40,80,81] The lipid sink mechanism has been suggested to be the predominant mechanism responsible for facilitating resuscitation.[24,66] Brent has gone as far as stating that lipid emulsion therapy should be attempted before resuscitation is abandoned in lipophilic drug-induced cardiotoxicity.[7] However, concerns have been raised whether lipid could interfere with the efficacy of amiodarone and other drugs used during resuscitation.[7]

Limitations and perspectives on lipid emulsion therapy for local anaesthetic cardiotoxicity

It should be emphasised that lipid therapy is an adjunct to and not a substitute for basic resuscitation measures. Failures of lipid rescue in local anaesthetic cardiotoxicity have not yet been reported. The prevention of inadvertent intravascular injection is of much greater importance than treatment of such a potentially devastating complication.[82]

Table III: Lipid rescue: the 10 main points of this article

1. Weinberg's laboratory-based animal research and subsequent case reports from other authors indicate that lipid emulsion therapy is an effective adjunct in the management of local anaesthetic cardiotoxicity.
2. This therapeutic modality represents a significant advance when considering prior poor outcomes after local anaesthetic (bupivacaine) cardiotoxicity.
3. The exact mechanism of how lipid emulsion exerts its beneficial effects in local anaesthetic toxicity is still unknown. Two major possibilities have been proposed, namely the lipid sink theory and the lipid flux theory.
4. So far, very few significant side effects of lipid rescue have been reported.
5. Given that local anaesthetic cardiotoxicity may be so difficult to treat, current authorities recommend initiating lipid infusion at the earliest signs of neuro- or cardiotoxicity, especially if bupivacaine has been used.
6. It should be emphasised that lipid therapy is an adjunct to basic resuscitation and not a substitute.
7. The use of propofol for its lipid solvent content in the setting of local anaesthetic toxicity may aggravate the situation and is not recommended.
8. Lipid infusions are most commonly available as a 500 ml bag of the 20% emulsion, which has a shelf life of 16 to 18 months. Initial treatment starts with a bolus of 1.5 ml/kg of the 20% emulsion over one minute, which may be repeated twice at five-minute intervals. Treatment with the rest of the bag should be completed over the following 20 to 30 minutes.
9. It is prudent to ensure that a stock of 1 000 ml of 20% lipid emulsion with attached dosage recommendations are readily available in all locations where local anaesthetic agents are administered.
10. The indications for lipid emulsion therapy are currently evolving to include cardiotoxicity from other lipophilic cardiotoxic drugs.

A negative aspiration test may falsely reassure the operator. The use of a nerve stimulator does not exclude the risk of accidental intravascular injection. The value of adding epinephrine to serve as an indicator of accidental intravascular injection represents an interesting debate. On the one hand, the addition of epinephrine to the local anaesthetic solution can provide an early indication of intravascular injection. On the other hand, the addition of epinephrine may add confusion as to the cause of the dysrhythmias[83] and delay definitive therapy. The importance of dose fractionation has been emphasised,[73] because it provides an early warning system and an opportunity to terminate the local anaesthetic injection at the first sign of toxicity. Slower injection of local anaesthetic decreases the maximal blood concentration. Prolonging the duration of an intravenous bolus of levobupivacaine from one to three minutes in sheep has been shown to reduce the peak plasma concentration by about 40%.[73] Nonetheless, whereas good technique will reduce the risk of toxicity it will not preclude it.

It should not be necessary to remind anaesthesiologists of the basic safety requirements (monitoring, resuscitation equipment and drugs – the latter including lipid emulsions) that should be available when performing regional blocks.[67] Nonetheless, we suspect that in most developing countries, many – if not most – regional blocks using bupivacaine are performed by orthopaedic surgeons and general practitioners. They would represent an important target audience for education on lipid rescue.

Conclusion

Corcoran and colleagues have reported that the incidence of local anaesthetic toxicity (7.5 to 20 per 10 000 peripheral nerve blocks and 4 per 10 000 epidurals) is declining, even as total number of blocks is increasing. While this may indicate a greater margin of safety, current opinion is that anaesthesiologists, in view of the devastating effects of bupivacaine on the myocardium, should ensure the availability of lipid and know how to use it. Whether the rapid evolution of this promising therapeutic modality will withstand the test of time remains to be seen (Table III).

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