Lipid emulsion in local anesthetic toxicity

Martyn Harvey\textsuperscript{a} and Grant Cave\textsuperscript{b,c}

\textbf{Purpose of review}
Enthusiasm for regional anesthesia has been driven by multimodal benefits to patient outcomes. Despite widespread awareness and improved techniques (including the increasing use of ultrasound guidance for block placement), intravascular sequestration and the attendant risk of local anesthetic systemic toxicity (LAST) remains. Intravenous lipid emulsion (ILE) for the treatment of LAST has been endorsed by anesthetic regulatory societies on the basis of animal study and human case report data. The accumulated mass of reporting now permits objective interrogation of published literature.

\textbf{Recent findings}
Although incompletely elucidated the mechanism of action for ILE in LAST seemingly involves beneficial effects on initial drug distribution (i.e., pharmacokinetic effects) and positive cardiotoxic and vasoactive effects (i.e., pharmacokinetic effects) acting in concert. Recent systematic review by collaborating international toxicologic societies have provided reserved endorsement for ILE in bupivacaine-induced toxicity, weak support for ILE use in toxicity from other local anesthetics, and largely neutral recommendation for all other drug poisonings. Work since publication of these recommendations has concluded that there is a positive effect on survival for ILE when animal models of LAST are meta-analyzed and evidence of a positive pharmacokinetic effect for lipid in human models of LAST.

\textbf{Summary}
Lipid emulsion remains first-line therapy (in conjunction with standard resuscitative measures) in LAST. Increasing conjecture as to the clinical efficacy of ILE in LAST, however, calls for high-quality human data to refine clinical recommendations.

\textbf{Keywords}
lipid emulsion, local anesthetic, resuscitation, toxicity

\section*{INTRODUCTION}
Regional anesthetic techniques continue to develop in light of recognized benefits over the entire perioperative course \cite{1–7}. Despite numerous measures to increase safety \cite{8–12}, systemic absorption and subsequent development of local anesthetic systemic toxicity (LAST) remains an ever-present concern for the practicing anesthesiologist. Incidence of LAST is variably described, with 67 separate events reported in literature between 2010 and 2014 \cite{13}. Morwald et al. \cite{14} report a 0.18\% rate of LAST in an administrative cohort of 238 473 patients undergoing joint arthroplasty between 2006 and 2014. Despite a decrease in overall rates of LAST during the observation period, use of lipid emulsion rose significantly (0.02–0.26\%) over the same interval for patients undergoing total knee joint replacement. In addition, overdose of nonlocal anesthetic medications vastly out-strip cases of LAST for clinicians also practicing in the field of critical care medicine \cite{15,16}.

First identified as an effective antidote in 1989 \cite{17}, lipid emulsion has gained widespread acceptance as the antidote of choice in LAST \cite{18–20}. Acknowledgment of the seemingly generic mechanisms of action for lipid emulsion has furthermore seen intravenous lipid emulsion (ILE) embraced by nonanesthesiologists and trialed in nonlocal anesthetic drug poisonings \cite{21–23}. Accumulated reports now present a considerable volume of data to evaluate lipid emulsion therapy and examine current recommendations. This article represents a critique of all state-of-the-art in this field.

\textsuperscript{*}Department of Emergency Medicine, Waikato Hospital, Hamilton, New Zealand, \textsuperscript{t}Department of Intensive Care Medicine, Tamworth Base Hospital, North Tamworth, New South Wales, Australia and \textsuperscript{t}School of Pharmacy, University of Auckland, Auckland, New Zealand

Correspondence to Martyn Harvey, Emergency Physician, Department of Emergency Medicine, Waikato Hospital, 3200, New Zealand.

Tel: +64 7 839 8899x95765; e-mail: martyn.harvey@waikatodhb.health.nz

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MECHANISMS OF LIPID EMULSION

Our evolving understanding of the pharmacologic sequelae following infusion of a concentrated lipid microemulsion can be broadly divided into effects on modulating drug distribution – that is, pharmacokinetic effects, and effects on cellular signaling and metabolic processing – that is, pharmacodynamics effects. Latterly, complex computational modeling techniques have allowed for integration of experimentally modeled discrete actions to be incorporated into a coherent whole explanation of ILE’s effect in LAST.

Pharmacokinetic effects

Since discovery of lipid emulsion as antidote, pharmacokinetic hypotheses have featured prominently in forwarded explanations of efficacy [17,24]. Early work by Weinberg et al. [25] demonstrated a significant reduction in myocardial bupivacaine content following perfusion of isolated rat hearts with perfusate containing lipid, a finding replicated by Chen et al. [26]. Subsequent authors have further demonstrated partitioning effects in vitro [27,28], in isolated tissue preparations [29–31], and in-vivo models of toxicity [32–34]. Initially coined the ‘lipid sink’ [35], both the moniker itself and the terminology used to describe the phenomenon of lipophilic toxins associating with a newly introduced intravascular lipid phase (e.g. ‘sequestration’, ‘binding’) conferred the erroneous notion of some permanence or even irreversibility. Extrapolation of this thesis largely underpinned enthusiasm for a role of ILE in general toxicity – wherein benefit was assumed purely on the basis of lipid to ‘suck’ highly lipophilic drugs away from the site of their toxic action and retain them in plasma [36,37].

Data from in-vivo studies, however, indicate the interaction of lipid soluble molecules with lipid microdroplets to be entropic – energy is neither consumed, nor released, when drugs of certain physicochemical characteristics associate with blood-borne lipid droplets [27]. As such bupivacaine, or any similarly lipophilic compounds, are free in their passive association with lipid droplets and will readily diffuse to tissues of higher affinity when presented. This change of thinking – that of lipid emulsion as a conduit to redistribution, rather than a sole ‘sink’ mechanism has brought about a change in nomenclature. Lipids’ pharmacokinetic action has been more aptly described as a ‘shuttle’ [38], or ‘subway’ [39] – with lipophilic drug akin to an aimless commuter free to ride, or alight, the ‘ILE carriage’ solely on the basis of subway/platform occupancy. Consideration of this analogy leads to very different interpretations of potential pharmacokinetic benefit when LAST is contrasted with oral ingestions of toxin (a far more common overdose situation). In LAST, induction of toxicity is expeditious, organ toxicity almost immediate, and introduction of lipid emulsion serves only to detoxify essential highly perfused organs (heart, brain) and shuttle toxin toward lesser occupied or perfused sites of deposition/metabolism (adipose tissue, muscle, liver) [40,41]. Conversely, early in enteric overdose the only ‘platform’ fully occupied is in the alimentary tract. In this scenario, the passive association of ILE for mesenterically presented toxin can only serve to increase gastrointestinal absorption and promote delivery to lesser occupied tissues – be they inert depots, or potential organ targets of toxicity, irrespective of type [42,43]. Conceivably, lipid may provide some pharmacokinetic advantage late in the course of enteric overdose when all platforms are saturated; circulation has contracted to essential organs only (or overt cardiac arrest is manifest), whereby lipid infusion may provide for a true low occupancy sump [44]. These as yet untested assumptions become significant in consideration for lipid emulsion recommendation following oral overdose.

Notably long-chain triglyceride preparations (e.g., Intralipid) have been experimentally demonstrated superior to mixed long/medium chain triglyceride preparations in exerting these pharmacokinetic effects [32].

Pharmacodynamic effects

Available data suggest pharmacokinetic mechanisms provide a necessary, but incomplete, explanation for the witnessed recovery of animals and humans suffering LAST. Direct positive effects on the intoxicated cardiovascular system in addition...
underpin lipid-mediated recovery from toxicity [33,45,46]. The fundamental mechanisms for these combined inotropic/vasopressor actions have been the subject of exhaustive study, yet consensus regarding the relative magnitude of each remains elusive. Lipid emulsion has been shown to reverse the bupivacaine-induced block of the fast Na current in rat left ventricular myocytes, using whole cell patch clamp techniques via both sink [47], and direct [48,49] effects. Lipid infusion has been furthermore hypothesized to overcome bupivacaine-induced impediments to mitochondrial acylcarnitine transferase activity (responsible for free fatty acid entry into mitochondria) and thereby cellular respiration [50]. Additional effects on insulin signaling have been reported with lipid emulsion modulating myocardial glucose handling by protein kinase B and S'adenosine monophosphate-activated protein kinase, resulting in favorable effects on insulinergic pathways and cardiac glycogen stores [51]. Apoptosis in h9c2 cardiomyocytes induced by bupivacaine may be reversed via lipid-mediated inhibition of the mitochondrial permeability transition pore (mPTP) with lipid significantly improving measures of mitochondrial function in vitro [52]. The ability of ILE to effect recovery from bupivacaine-induced astylole in rats was prevented by high-dose naloxone administration and by selective δ-opioid and κ-opioid (but not μ-opioid) receptor antagonists in whole rats [53]. Hypothesized mechanisms for this observation include opioid receptor-mediated signaling pathways that ultimately inhibit mPTP pore opening.

Local anesthetics such as bupivacaine cause vasoconstriction at low dose, and vasodilation at toxic dose [54,55], mediated by a decrease in either the intracellular calcium concentration, or calcium sensitization [56]. A role for lipid-mediated reversal of bupivacaine-induced peripheral vasodilation has in addition been forwarded. Heinonen et al. [30] demonstrated 4 ml/kg 20% Intralipid to reverse bupivacaine-induced cardiovascular depression in anesthetized swine. Hemodynamic improvements were largely associated with increased systemic vascular resistance, and despite demonstrating both modest sink effects and a 30% increase in lipid-based myocardial mitochondrial respiration, cardiac index failed to improve. Similar benefits were not observed in a near identical pig model of levobupivacaine-induced cardiotoxicity complicated by hypoxemia and acidosis when 20% Intralipid was administered at 1.5 ml/kg followed by a infusion of 0.25 ml/kg/min for 29 min in accord with current treatment guidelines [57]. Inadequate dosing, and pH-mediated increases in myocardial ion trapping along with reduced affinity of ionized local anesthetic for circulating lipid, may have contributed to observed treatment failure – underscoring the need for adequate basic resuscitation measures (oxygenation, cardiopulmonary resuscitation) in conjunction with specific antidotal treatments in management of LAST.

In addition to direct partitioning effects, lipid emulsions have been shown to reverse bupivacaine-induced vasodilation by a number of mechanisms. Bupivacaine-induced inhibition of protein kinase C and CPI-17 (a phosphorylation-dependent inhibitory protein of myosin) has been demonstrated to induce vasodilation in isolated rat aorta – and is itself attenuated following application of lipid emulsion [58]. Consistent with partitioning coefficients, this reversal appears dependent on the intrinsic lipid solubility of the offending local anesthetic. Mild-preacidification has furthermore been demonstrated to enhance lipid emulsion-mediated reversal of toxic dose levobupivacaine-induced vasodilation in endothelium-intact rat aorta via the inhibition of nitric oxide synthase [59].

Computational modeling techniques have been employed to integrate the seemingly disparate proposed actions of lipid emulsions into coherent whole explanations of the mechanism of lipid rescue. Using a pharmacokinetic-pharmacodynamic model, Fettiplace et al. [46] demonstrated the rapid recovery of hemodynamic stability after bupivacaine poisoning in rats to depend on lipid-mediated direct cardiotoxic action, increased blood volume, and pharmacokinetic effects acting in concert. The same investigative group subsequently provided the most comprehensive explanation to date for the effect of triglyceride microemulsion in bupivacaine pharmacotoxicity by combining physiologic parameters with pharmacokinetic data obtained from bupivacaine-intoxicated rats in an in-silico computational model [33]. This work demonstrated a rapid initial detoxifying effect of lipid emulsion, acting primarily on key end-organs, including the heart and the brain – depending on the partitioning effect of introduced lipid. Once cardiac drug concentration fell below a threshold (consistent with binding thresholds for bupivacaine), the emulsion produced a cardiotonic effect through the combined actions of increased blood volume and an increase in myocardial contractility. Subsequently, increased blood carriage combined with improved cardiac output was demonstrated to enhance redistribution of drug to non-essential depot organs and sites of metabolism.

**EVALUATION OF LIPID EMULSION**

Clinical rarity and barriers to experimental replication are impediments to randomized human study...
of LAST. Nevertheless, the effect of infused lipid emulsions on elimination kinetics and early onset neurologic toxicity has been evaluated in two volunteer studies. Heinonen et al. [60] reported no difference in subjectively reported, nor electroencephalographic measures, of central nervous toxicity in healthy volunteers undergoing lidocaine injection following Intralipid infusion. A modest reported pharmacokinetic benefit of lipid was in keeping with lidocaine’s log P. In a similar experiment, Dureau et al. [61] reported no difference in dose to first onset neurotoxicity when the local anesthetics ropivacaine and levobupivacaine were confused with lipid emulsion. Lesser reported $C_{\text{max}}$ and increased central volume of distribution supported a modest partitioning effect for ILE. Modeling based on parameters derived from this experiment suggested lipid emulsion would exert beneficial pharmacokinetic effects in the setting of rapidly rising local anesthetic concentrations.

Since the first case report outlining successful lipid resuscitation from local anesthetic (bupivacaine/mepivacaine)-induced cardiac arrest in 2006 [62], and recovery from nonlocal anesthetic (bupropion/lamotrigine) overdose in 2008 [63], numerous subsequent reports of successful lipid rescue have been published in anesthetic and general toxicology literature. Many high-quality systematic reviews on the subject have catalogued individual case reports and case series [13,44,64–66], and registry-based datasets [67], in a largely descriptive fashion. Case reporting is, however, inherently subject to reporter and publication bias (both positive and negative), and individual instances of lipid emulsion administration heterogenous in regards patient characteristics, toxin dose and administration, adjuvant resuscitation treatments employed, and reporting of clinical and biochemical outcomes. Despite absence of standardization in reporting (which should be possible in LAST – if not nonlocal anesthetic poisoning), accumulated case report data has reached critical mass such that critical evaluation of large numbers of ‘like’ reports has now been undertaken [68**,69**,70].

In 2014, the American Academy of Clinical Toxicology (AACT) initiated a collaboration between the European Association of Poison Centres and Clinical Toxicologists, The Asia Pacific Association of Medical Toxicology, The Canadian Association of Poison Control Centres, The American College of Medical Toxicology and the American Association of Poison Control Centers to create the Lipid Emulsion Therapy in Clinical Toxicology Workgroup (hitherto referred to as the Workgroup). Comprising anesthesiologists, toxicologists, emergency and critical care physicians, and pharmacists the workgroup was tasked with evaluation of all relevant reports (both local anesthetic and nonlocal anesthetic) pertaining to the use of lipid emulsion in toxicology. The ultimate goal of the workgroup was to comprehensively evaluate all relevant reports and make evidence-based recommendations based on a two-round modified Delphi method [71]. Following review of 113 reports of ILE use in local anesthetic toxicity (76 human reports, 38 animal studies) the local anesthetic workgroup concluded that ‘ILE appears to be effective for reversal of cardiovascular or neurological features in some cases of local anesthetic toxicity, but there is currently no convincing evidence, showing that ILE is more effective than vasopressors or to indicate, which treatment should be instituted as first-line therapy in severe local anesthetic toxicity’. The available evidence was adjudged of very low quality, confined to animal experiments and human and animal case reports or series [68**]. In a similar, yet less rigorously conducted report [70], lipid emulsion was deemed causal in recovery of only three of 36 reports of human LAST with some ‘certainty’.

The workgroups nonlocal anesthetic arm reviewed 203 articles (141 human reports, 62 animal reports) and concluded the effect of ILE in various nonlocal anesthetic poisonings is heterogenous, and the quality of evidence similarly remains low to very low [69**]. Workgroup endorsement for ILE treatment [72**] was made in the setting of: bupivacaine-induced cardiac arrest; life-threatening bupivacaine toxicity as part of treatment modalities, and when other therapies fail/in last resort; and in life-threatening toxicity induced by non-bupivacaine local anesthetics if other therapies fail/in last resort; and in life-threatening amitriptyline or bupropion toxicity if other therapies fail/in last resort. In light of reports such as these, some investigators with significant experience in the specialty have even suggested that there is insufficient evidence to support a role for lipid emulsion in LAST, let alone other poisonings [73,74]. Responding to some of the original local anesthetic workgroup conclusions, Fettiplace and McCabe [75] re-extracted and quantitatively analyzed outcomes of animal data in local anesthetic toxicity. They offer different interpretation to those of the workgroup citing a significant reduction the odds of death across all resuscitative models (odds ratio $=0.24$) when ILE was analyzed as an independent variable in resuscitation from LAST in animal models. Quantification of effect, and extra precision in abstraction of experimental outcomes, lend significant weight to their interpretation of the same data.

In sum, it would appear that areas of controversy remain regarding the use of lipid therapy in LAST
(other poisonings notwithstanding). These questions may only be possible to definitively answer with human studies or high-quality registry data with rigorous reporting criterion. Further confounding the issue of lipid emulsion therapy is the increasing recognition of adverse sequelae associated with use [76**]. Unwanted reactions to lipid emulsions have proven rare in healthy volunteers undergoing lipid infusion according to current treatment guidelines [60,77]. Lipid emulsions have, however, been associated with pancreatitis [78,79], acute respiratory distress syndrome [80], interference with laboratory analyses [81], and extracorporeal circuit compromise in hemodialysis [82,83] and extracorporeal membrane oxygenation [84].

**FUTURE OF LIPID EMULSION**

Greater understanding of the mechanisms of ILE is likely to facilitate advances in recommendations for use. Evaluation of treatment regimens to optimize both formulations (20 vs. 30% lipid preparations), dosing volumes, and rapidity of infusion are required in appropriate animal models. Development of second-generation lipid-based detoxifying antidotes, such as liposomal preparations [85], and more recently pH gradient liposomes designed to utilize toxin ionization to trap drugs within the liposome core [86,87], may provide superior agents for drug entrapment. Absence of any pharmacodynamic action with these newer pure drug scavengers may in part explain lesser observed antidotal effects when compared with standard ILE in some animal models [88]. However, perhaps the greatest step forward will come with establishment of high-quality and standardized reporting of all LAST cases to appropriate registries and from randomized trials in humans.

**CONCLUSION**

Use of lipid emulsions in LAST has become widespread following nearly 2 decades of basic science and case report data purporting benefit. Accumulation of a critical mass of literature, enabling systematic evaluation of evidence for ILE in LAST, has suggested that indications are conditional, and areas of controversy remain. Indications for lipid emulsions in nonlocal anesthetic poisoning are even less clear. Despite significant impediments, refinement to recommendations for lipid emulsion will be best driven by structured analysis of quality registry data or controlled human evaluation.

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*Use of lipid emulsions preparations including Intralipid for any toxicologic emergency is an off-label indication per FDA.*

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of outstanding interest
- of special interest

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41. Harvey M, Cave G, Ong B. Intravenous lipid emulsion-augmented plasma protein binding, and cardiovascular response in a rabbit model of cardiac arrest or life-threatening toxicity, and for nonbupiva-caine local anesthetic toxicity when other therapies fail or in last resort. The workgroup issued neutral recommendations for almost all other cardiac arrest/ life-threatening overdose scenarios in keeping with their self-described ‘caution to make recommendations for or against a therapy where so little moderate or high quality human data exist’.


49. AACT initiated Lipid Emulsion Therapy Workgroup report on systematic evaluation of all published reports of lipid emulsion treatment in local anesthetic toxicity. The most comprehensive review of its type undertaken to date.


51. AACT initiated Lipid Emulsion Therapy Workgroup report on systematic evaluation of all published reports of lipid emulsion use in local anesthetic toxicity. AACT initiated Lipid Emulsion Therapy Workgroup report on systematic evaluation of all published reports of lipid emulsion use in local anesthetic toxicity.