Lipid resuscitation for local anesthetic toxicity: is it really lifesaving?
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Introduction
Local anesthetic systemic toxicity (LAST) is a rare but potentially catastrophic complication of regional anesthesia [1]. Laboratory findings made over the last decade and recent case reports suggest that lipid emulsion is a potential antidotal treatment and might reduce the morbidity of this complication. Weinberg et al. [2] first reported in 1998 that lipid emulsion infused during resuscitation increased the median lethal dose (LD₅₀) of bupivacaine in rats by 50%. In a subsequent study [3] of bupivacaine-induced cardiac arrest in dogs, treatment with lipid improved hemodynamics and survival compared with isotonic saline-treated controls. This review will summarize clinical experience with lipid emulsion, highlight relevant laboratory studies and address the current status of this therapy with respect to timing, dose, potential adverse effects and its overall role in resuscitation.

Clinical experience
In 2006, Rosenblatt et al. [4] and Litz et al. [5] reported successful clinical use of lipid emulsion to reverse local anesthetic-induced cardiac arrest. In both cases, the patients failed to respond to standard resuscitation methods but regained normal hemodynamic parameters shortly after lipid emulsion infusion. Further clinical reports [6,7••–10••] have provided a growing body of support for use of this therapy. Lipid emulsion has been used to treat LAST due to bupivacaine, levobupivacaine, ropivacaine and mepivacaine, alone or in combination. Lipid preparations other than Intralipid have also been found to be effective; the successful use of 20% Liposyn III (Hospira, Inc., Lake Forest, Illinois, USA) [10••] and 20% Medialipid (Braun, Kronberg, Germany) [8••] has been reported. In addition to case reports published in peer-reviewed journals, many cases have been posted at the educational website www.lipidrescue.org.

Purpose of review
Laboratory studies and clinical reports have led to the acceptance of lipid emulsion as an effective treatment of local anesthetic-induced cardiac arrest. This review discusses subsequent clinical reports, relevant laboratory studies and topics for further research.

Recent findings
Case reports have confirmed the efficacy of lipid resuscitation for local anesthetic systemic toxicity. Furthermore, lipid emulsion has been used with apparent success early in the spectrum of local anesthetic systemic toxicity to preempt cardiac arrest. The role of lipid emulsion has expanded to treatment of cardiac toxicity due to other lipophilic drugs. This appears to have an acceptable safety profile, although elevated amylase has been reported. Laboratory investigations in animals suggest that concomitant hypoxemia hinders resuscitation attempts, and that epinephrine and vasopressin are more likely to be associated with poor outcomes than lipid.

Summary
Lipid emulsion infusion appears to be an effective treatment for cardiac toxicity induced by lipophilic medications. Given the difficulties of performing clinical trials, further laboratory investigation and clinical correlation are needed to better define its role in resuscitation.

Keywords
lipid emulsion, local anesthetics, resuscitation, toxicity
2 Regional anaesthesia

potentially toxic doses of local anesthetics are administered; recommended doses were provided (http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf). In 2008, the American Society of Critical Care Anesthesiologists and the American Society of Anesthesiologists Committee on Critical Care Medicine as well as the Resuscitation Council of the UK also published protocols for treatment of LAST, which incorporated the use of lipid emulsion (http://www.asahq.org/clinical/Anesthesiology-CentricACLS.pdf, http://www.resus.org.uk/pages/caLocalA.htm). Of note, propofol is not a substitute for lipid emulsion, given its lower lipid content and the known myocardial depressant effects.

Application to other toxic events
Animal studies have demonstrated efficacy of lipid emulsion in treating verapamil toxicity [11,12], clomipramine toxicity [13] and propranolol toxicity [14]. Furthermore, lipid infusion has recently been used by physicians treating patients for overdoses of other lipophilic toxins. For instance, Sirianni et al. [15*] reported the dramatic case of a 17-year-old girl with a severe overdose of bupropion and lamotrigine. She subsequently suffered a prolonged cardiac arrest refractory to standard advanced cardiac life support (ACLS), including multiple defibrillations and bolus doses of epinephrine, NaHCO₃, amiodarone and ‘wide-open’ infusions of dopamine, norepinephrine and epinephrine. One minute after an infusion of 100 ml of 20% lipid emulsion, she regained normal circulation and vital signs. Her hospital course was complicated by acute lung injury (ALI) that was apparent prior to the lipid infusion, and she was eventually discharged with only minor memory deficits.

As the authors point out, bupivacaine and bupropion share similar properties, including sodium channel blocking actions and nearly identical octanol:water partition coefficients. Subsequent reports have described the successful use of lipid rescue in the treatment of circulatory and neurological symptoms of overdose with sertraline and quetiapine (coma) [16*], sustained-release verapamil (hypotension) [17*] and haldol (torsades de pointes) [18*]. An animal study [19*] of verapamil overdose indicates that similar doses of lipid (in terms of total lipid mass) were necessary as were used to treat bupivacaine-induced asystole in rats.

Challenges in investigation
The infrequency of severe LAST cases and ethical considerations preclude randomized clinical trials of lipid resuscitation. We must, therefore, rely on case reports and laboratory investigations to inform clinical practice. However, case reports suffer from positive reporting bias and provide neither a precise numerator nor denominator of cases. Although early clinical reports may have been questioned because recovery might have resulted from delayed response to conventional treatment rather than lipid emulsion, the reliably rapid clinical improvement after administration of lipid in dozens of cases appears to support its efficacy. Taken together, the growing number of cases and the highly consistent clinical descriptions of return of spontaneous circulation strongly support the usefulness of this therapy. This contrasts with classical descriptions of refractory cardiac arrests in similar circumstances.

One current challenge is to define the role of lipid emulsion in the treatment of toxicity induced by lipophilic agents. New information is inevitably followed by new questions. Issues that remain to be determined include optimal timing of administration and dose, potential adverse effects and the place of lipid in the scheme of resuscitation.

Timing of administration
Current protocols from the AAGBI (and www.lipidrescue.org) recommend lipid emulsion for cardiac arrest in conjunction with standard basic life support (BLS) and ACLS practices (http://www.lipidrescue.org, http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf). However, as lipid therapy has become more accepted, clinicians have chosen to administer lipid emulsion earlier in the spectrum of adverse local anesthetic reactions, preferring to act before refractory cardiac arrest occurs. For instance, lipid emulsion was used to treat central nervous system (CNS) toxicity and ventricular ectopy in an attempt to prevent progression to cardiac arrest [6]. Other examples include a 13-year-old girl who developed ventricular tachycardia after lumbar plexus block with a ropivacaine–lidocaine mixture. Lipid emulsion was administered at the onset of arrhythmia; the electrocardiogram reverted to normal, and surgery was performed uneventfully [8*]. A 91-year-old man became unresponsive with extrasystoles after upper extremity regional anesthesia with meprivacaine and prilocaine. He received lipid emulsion, with subsequent restoration of consciousness and resolution of ectopy [9*]. Similarly, lipid reversed CNS symptoms and ventricular tachycardia in an 82-year-old woman after lower extremity nerve block [7*]. A parturient who developed agitation and inability to follow commands after epidural with bupivacaine was successfully treated with lipid emulsion [20].

Effective dose
Case reports indicate that currently proposed dose regimens are efficacious, although it is certainly possible that there are treatment failures that have not been reported. For local anesthetic-induced cardiac arrest,
recommendations include a bolus of 20% lipid, 1.5 ml/kg (http://www.lipidrescue.org, http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf, http://www.resus.org.uk/pages/caLocalA.htm) followed by an infusion of 0.25 ml/kg/min for 20 min (http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf), 30–60 min (http://www.lipidrescue.org) or until stable rhythm is restored (http://www.resus.org.uk/pages/caLocalA.htm). If adequate circulation is not restored, various regimens have been suggested: bolus doses may be repeated up to two times (http://www.lipidrescue.org), up to two times at 5 min intervals (http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf) or at 5 min intervals until stable rhythm is restored (http://www.resus.org.uk/pages/caLocalA.htm), and the infusion rate may be increased (http://www.lipidrescue.org) or increased to 0.5 ml/kg/min for 10 min (http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf). Marwick et al. [21**] reported recurrence of ventricular ectopy in a 72 kg man who was successfully treated with Intraplaid for bupivacaine-induced cardiac arrest. A 150 ml bolus was initially administered, followed by 350 ml over the next 30 min. Sinus rhythm and hemodynamic stability were restored, and surgery proceeded, but 40 min later, ventricular ectopy recurred. They point out that a full 1000 ml of lipid may be required. On the contrary, in a study [8†] describing lipid treatment of ventricular tachycardia after nerve block, the bolus dose alone was adequate and infusion was unnecessary.

Adverse effects

There are concerns regarding possible adverse effects of lipid therapy. The risk–benefit ratio becomes particularly important when lipid emulsion is used in patients prior to the onset of overt hemodynamic instability and cardiac arrest. The most serious adverse effect that has been associated with the use of lipid emulsion for parenteral nutrition is pulmonary injury.

Recently, a single elevated amylase level was reported in the patient described by Marwick et al. [21**] above; the patient had received a total of 500 ml of Intraplaid. No clinical signs of pancreatitis were noted, and no specific treatment was needed. Whether other cases of hyperamylasemia have occurred or are underreported is not known. Notably, no other adverse effects have been reported with the use of lipid for the treatment of drug-related toxicity. Again, this may reflect underreporting or positive bias; long-term follow-up may reveal problems that are not currently apparent.

Laboratory investigations

In order to better define the place of lipid emulsion in resuscitation, Weinberg et al. [22**] studied lipid versus epinephrine in a rat model of cardiac arrest. Anesthetized rats received bupivacaine, 20 mg/kg, to induce asystole, then immediately received cardiopulmonary resuscitation (CPR) with 100% oxygen and either 30% lipid, 5 ml/kg bolus and 0.5 ml/kg/min infusion, epinephrine, 30 µg/kg bolus or normal saline. Bolus doses of medications were repeated at 2.5 and 5 min until the rate pressure product was above 20% of baseline. At 10 min, resuscitation rates were 5/5, 4/5 and 0/5 in the lipid group, epinephrine group and saline group, respectively; pH, pO2 and saturated venous oxygen (SvO2) were higher and lactate lower in the lipid group. Notably, an early increase in blood pressure (BP) with epinephrine was followed by subsequent decline and pulmonary edema, not seen in the lipid group. In a similar follow-up study [23**], lipid emulsion was superior to vasopressin and vasopressin/epinephrine with respect to rate pressure product, pH, SvO2 and lactate. Results with vasopressin alone were particularly unfavorable. In a rat model of bupivacaine-induced asystole, concomitantly administered epinephrine above 10 µg/kg hindered resuscitation [24**]. These data suggest that use of lipid emulsion earlier in the resuscitative effort and avoidance of pressors may result in better outcomes in this setting. These are preliminary findings in animals, however, which need to be investigated further and confirmed prior to extrapolating to the clinical setting.

Of interest, the patient described by Sirianni et al. [15**] above, who received multiple doses of epinephrine (18 mg total), had postresuscitation pulmonary edema/ALI. Although pulmonary edema may occur after resuscitation from cardiac arrest treated with standard ACLS protocols, the consistent pattern of postvasopressor pulmonary edema and worsened recovery in the pressor-treated animals in the above-mentioned investigations is notable. Whether this phenomenon is particular to the rat model, whether bupivacaine somehow predisposes to ALI or whether this results from significant myocardial poisoning by local anesthetic and the vasoconstriction caused by vasopressin and epinephrine which then overwhelms the weakened ventricle leading to severe failure remains to be elucidated in further studies.

Despite an apparent general enthusiasm for lipid resuscitation, several reports question its efficacy with respect to vasopressor treatment. Mayr et al. [25**], working with a porcine model of bupivacaine overdose, reported that vasopressin combined with epinephrine resulted in higher coronary perfusion pressure during CPR and better short-term survival rates than lipid emulsion. In this model, mechanical ventilation was stopped after anesthetized animals received 0.5% bupivacaine, 5 ml/kg, then not resumed until 1 min after asystole occurred, at which time CPR was initiated and mechanical ventilation resumed. Animals received either 20% Intralipid (4 ml/
kg, followed by infusion of 0.5 ml/kg/min) or vasopressin/epinephrine (every 5 min in escalating doses, 0.4/45, 0.4/45 and 0.8/200 units/kg and μg/kg). Return of spontaneous circulation, defined as SBP of at least 80 mmHg for at least 5 min, was obtained in 5/5 of the pressor group but 0/5 of the lipid group. The authors note that, in this short-term study, they might have missed survival at a later time among the lipid group. The design of the study, however, raises the question of whether the cardiac arrest was bupivacaine-induced or hypoxemia-induced in the context of bupivacaine toxicity.

In contrast to perioperative occurrences in which the cause is known, emergency rooms receive patients presenting with cardiopulmonary and neurologic compromise of unknown cause. Physicians need to decide whether to administer lipid without knowing definitively whether the patient had ingested a lipophilic toxin. It is, therefore, important to know whether lipid itself interferes with standard resuscitation. Harvey et al. [26**] addressed this question in a rabbit model of asphyxial cardiac arrest. The endotracheal tube was cross-clamped to cardiac arrest. Animals were randomized to normal saline versus 20% Intralipid, 3 ml/kg. Resuscitation included BLS/ACLS with defibrillation and epinephrine, 100 μg/kg, repeated if needed. Lipid emulsion/ACLS resulted in lower coronary perfusion pressure and lower rates of return of spontaneous circulation (1/12 versus 7/11) compared with ACLS alone. Of interest, however, at 50 min, there was no difference in survival between groups.

What can we conclude from these conflicting studies? First of all, the critical importance of prompt airway management and maintenance of adequate oxygenation cannot be overstated. The abysmal outcomes in the study by Harvey et al. [26**] reinforce the importance of the ‘A’ and ‘B’ of the ‘ABC’s’ – airway, breathing and circulation. The reports of successful use of lipid rescue are likely at least partly predicated on these being ‘witnessed’ events and the resulting absence of significant hypoxemia as a contributing factor. These reports generally describe appropriate airway management at the first sign of CNS irritability, ventricular ectopy or hemodynamic instability, with supplemental oxygen, ventilation and intubation when necessary. The study of Mayr et al. [25**] describes a somewhat different scenario. On the contrary, if documentation of lipophilic toxin ingestion is lacking and hypoxemia is present, the data by Harvey et al. [26**] would argue against lipid use. Finally, in cases of known LAST complicated by significant hypoxemia, the data by Harvey et al. [26**] might caution against earlier use of lipid; however, the poor 50 min survival in both groups suggests there is still much room for research as the hypoxemia is likely more damaging than the lipid. The poor overall survival is consistent with that noted in studies of out-of-hospital cardiac arrest [27*].

**Mechanism**

Insights into the mechanism of action of lipid emulsion will aid in optimizing its use. At present, the most likely theory appears to be that of the lipid ‘sink’ binding the lipophilic drugs and thereby reducing tissue content of the toxin. Plasma levels are difficult to obtain during resuscitation, however, and results so far are inconsistent. An in-vitro study did indeed demonstrate high solubility of local anesthetics in lipid emulsions and high binding capacity of these emulsions; interestingly, Intralipid appeared about 2.5 times more efficacious than Medialipid and binding was reduced at lower pH [28*].

**Conclusion**

Lipid emulsion has an apparently acceptable safety profile in currently recommended doses and appears to be effective in the treatment of cardiac arrest resulting from lipophilic toxins. Clinicians report successful, early administration of lipid emulsion to preempt cardiac arrest. Continued diligent observation and reporting by clinicians as well as appropriate laboratory investigation will lead to better information and understanding of the precise role of lipid emulsion in resuscitation.

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**References and recommended reading**

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

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1 Albright G. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979; 51:285–287.
Lipid resuscitation

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This study describes use of lipid emulsion to successfully treat CNS signs and ventricular tachycardia with a pulse in a patient after nerve block.


This study describes the successful use of Medialipid to treat a 10-year-old girl who developed ventricular tachycardia after lumbar plexus block with ropivacaine.


This study describes the successful use of lipid emulsion to reverse CNS signs and treat ventricular ectopy in a patient who received brachial plexus block.


This study describes the successful use of Liposyn III to treat cardiac arrest after brachial plexus block.


This study describes the first clinical use of lipid emulsion to treat a patient with toxicity due to lipophilic medications other than local anesthetics.


This study describes the use of lipid emulsion to reverse coma in a patient with drug overdose.


This study describes the use of lipid emulsion to treat hypotension due to overdose of sustained-release verapamil.


This study describes the successful use of lipid emulsion to treat pulseless multiform ventricular tachycardia resulting from administration of haloperidol.


In this animal study of treatment of verapamil toxicity, the optimal dose of lipid was approximately 18 mg/kg.


This study describes a patient who developed recurrence of ventricular ectopy 40 min after successful resuscitation from cardiac arrest with lipid. Amylase was elevated postoperatively, but no signs of pancreatitis were noted.


This study of bupivacaine-induced cardiac arrest in a rat model found that lipid was superior to epinephrine with respect to resuscitation rates and metabolic parameters.


This study in a rat model found that lipid was superior to vasopressin and epinephrine for resuscitation of bupivacaine-induced cardiac arrest.


In this study of bupivacaine-induced cardiac arrest in a rat model, epinephrine more than 10 μg/kg hindered resuscitation.


In this study of bupivacaine toxicity in a porcine asphyxial model, vasopressin/epinephrine resulted in a better short-term survival than lipid emulsion.

26 Harvey M, Cave G, Kazemi A. Intralipid infusion diminishes return of spontaneous circulation than ACLS/lipid emulsion.


In this large study of epinephrine/vasopressin versus epinephrine alone for out-of-hospital cardiac arrest, there were no significant differences between groups in survival to hospital admission (approximately 21%) or survival to hospital discharge (approximately 2%).


This in-vitro study demonstrated high solubility of local anesthetics in lipid emulsion and high binding capacity of lipid emulsions.