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Corresponding author:
Ju-Tae Sohn, M.D.
Department of Anesthesiology and Pain Medicine, Gyeongsang National University Hospital, 79 Gangnam-ro, Jinju 52727, Korea
Tel: +82-55-750-8586
Fax: +82-55-750-8142
Email: jtsohn@gnu.ac.kr
ORCID: https://orcid.org/0000-0003-0102-5800

Mechanisms underlying lipid emulsion resuscitation for drug toxicity: a narrative review

Soo Hee Lee[1,2,3], **Ju-Tae Sohn**[3,4]

Department of Anesthesiology and Pain Medicine, [1]Gyeongsang National University Changwon Hospital, Changwon, [2]Gyeongsang National University College of Medicine, [3]Institute of Health Sciences, Gyeongsang National University, [4]Department of Anesthesiology and Pain Medicine, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Jinju, Korea

Currently, lipid emulsion (LE) is widely used to treat local anesthetic systemic toxicity (LAST). LE also ameliorates intractable cardiovascular collapse caused by lipid-soluble non-local anesthetic drug toxicity. This review aims to provide the underlying mechanism of LE resuscitation in drug toxicity (including LAST) and a detailed description of LE treatment and to discuss further research directions. We searched for relevant articles using the following keywords: "local anesthetic systemic toxicity or LAST or toxicity or intoxication or poisoning" and "Intralipid or lipid emulsion." The underlying mechanisms of LE treatment can be classified into indirect and direct effects. One indirect effect known as the lipid shuttle is a commonly accepted mechanism of LE treatment. The lipid shuttle involves the absorption of highly lipid-soluble drugs (e.g., bupivacaine) from the heart and brain through the lipid phase, which are then delivered to the muscle, adipose tissue, and liver for storage and detoxification. The direct effects include inotropic effects, fatty acid supply, attenuation of mitochondrial dysfunction, glycogen synthase kinase-3β phosphorylation, and inhibition of nitric oxide. These mechanisms appear to act synergistically to treat drug toxicity. The recommended protocol for LE treatment of LAST is as follows: a bolus administration of 20% LE at 1.5 ml/kg over 2–3 min followed by 20% LE at 0.25 ml/kg/min. LAST most commonly occurs after intravenous administration of local anesthetics. However, non-local anesthetic drugs that cause drug toxicity are orally administered. Further studies are needed to determine the optimal dosing schedule of LE treatment for non-local anesthetic drug toxicity.

Keywords: Drug; Intravenous fat emulsions; Local anesthetics; Poisoning; Therapeutics; Toxicity.

Introduction

Although the incidence rate of local anesthetic systemic toxicity (LAST) is low (e.g., the cumulative incidence rate of LAST due to the peripheral nerve block in total hip arthroplasty was reported to be 0.18%), it is often fatal [1]. In addition, a large proportion (up to 50%) of cases of LAST are caused by non-anesthesiologists [2]. The initial clinical symptoms of LAST involve the central nervous system (i.e., anxiety, dizziness, tinnitus, dysgeusia, and seizures) and are usually followed by cardiovascular collapse, including arrhythmia, hypotension, and cardiac arrest [3]. Efforts to prevent the occurrence of LAST through the use of ultrasound, minimal effective dosage of local anesthetics, aspiration techniques at the injection site, and mixing epinephrine with local anesthetics during ad-

ministration can contribute to reducing the incidence of LAST; however, the risk cannot be eliminated [4]. Newborn, infant, and elderly patients and those with cachexia; hypoalbuminemia; metabolic abnormalities; mitochondrial disease; and cardiac, liver, or kidney dysfunction have a higher risk of developing LAST than young, healthy individuals [2]. Thus, even when local anesthetics are administered at acceptable doses, LAST can still occur in these patients [2]. The prevention of LAST is more important than its treatment. With the recent increase in the use of peripheral nerve blocks, which are associated with a relative increase in the incidence of LAST, clinician's awareness of the prevention and treatment of LAST has increased [5].

In 1961, commercially available lipid emulsion (LE), which is derived entirely from soybean, was initially developed for parenteral nutrition [6]. LE is currently also used as a solvent for propofol and etomidate and to treat drug toxicity, including LAST. In three steps, long-chain fatty acids are transported to cardiac mitochondria from the cytoplasm and subsequently used to produce adenosine triphosphate (ATP) [7]. Long-chain fatty acyl-CoA synthase in the cytoplasm produces long-chain fatty acyl-CoA from long-chain fatty acids [7]. First, carnitine palmitoyltransferase I produces long-chain fatty acylcarnitine from long-chain fatty acyl-CoA and carnitine in the cytoplasm [7]. Second, carnitine acylcarnitine translocase transports long-chain fatty acylcarnitines from the cytoplasm to the cardiac mitochondria [7]. Third, carnitine palmitoyltransferase II splits the long-chain fatty acylcarnitines in the cardiac mitochondria into long-chain fatty acyl-CoA and carnitine, which is then returned to the cytoplasm from the cardiac mitochondria (carnitine shuttle) [7]. Long-chain fatty acyl-CoA in cardiac mitochondria contributes to ATP production through fatty acid β-oxidation and the tricarboxylic acid cycle [7].

The following reports introduced in this review have greatly contributed to advances in LE treatment for LAST [8–10]. Bupivacaine administered at below-toxic doses (0.36 mg/kg; maximal recommended dose of bupivacaine with epinephrine, 2 mg/kg) as a tumescent solution for axillary liposuction was reported to produce complex ventricular arrhythmia in a patient with secondary carnitine deficiency due to isovaleric acidemia [8]. As the carnitine shuttle is involved in delivering long-chain fatty acids to cardiac mitochondria, which subsequently contributes to ATP production, secondary carnitine deficiency leads to impaired production of ATP derived from long-chain fatty acids in cardiac mitochondria [7]. Since bupivacaine inhibits carnitine acylcarnitine translocase in cardiac mitochondria, the ventricular arrhythmia induced by the below-toxic dose of bupivacaine observed in this patient seems to have resulted from an increased susceptibility to bupivacaine-induced cardiotoxicity due to secondary carnitine deficiency [7–9]. Weinberg et al. [10] reported the first laboratory study in which LE pretreatment resulted in an increase in the bupivacaine dosage necessary to induce bupivacaine-induced cardiac arrest in rats, resulting in an increase in the bupivacaine content in the lipid phase of the plasma and lipid mixture. This report suggests that lipid-soluble bupivacaine (log P = log [octanol/water partition coefficient]; log P = 3.41) is absorbed in the lipid phase of LE [10]. The first clinical case of successful LE treatment for persistent cardiac arrest caused by the local anesthetics bupivacaine and mepivacaine used for an interscalene block was reported in 2006 [11]. Two years later, the first clinical case of successful LE resuscitation in intractable cardiac arrest caused by the toxicity of the non-local anesthetic anti-depressant drug bupropion (log P = 3.6) and the anti-convulsant lamotrigine (log P = 1.93) was reported [12]. LE is currently recommended for the treatment of LAST by the American Society of Regional Anesthesia and Pain Medicine [2]. LE administration during LAST is currently performed at an earlier stage compared with the past [2]. Moreover, LE as an adjuvant drug has been reported to alleviate cardiovascular collapse and central nervous system symptoms caused by non-local anesthetic drugs with high lipid solubility (log P > 2) that are unresponsive to supportive treatment [13–15]. Thus, this review aimed to provide the underlying mechanism of LE resuscitation in drug toxicity (including LAST) and a detailed description of LE treatment and to discuss further research directions.

Methods

We conducted a search of PubMed for related articles published until July 31, 2022 using the following keywords: "local anesthetic systemic toxicity or LAST or toxicity or intoxication or poisoning" and "Intralipid or lipid emulsion." Among the articles retrieved, which included animal and clinical experiments, case reports, letters, and reviews, the articles relevant to LE treatment for drug toxicity caused by local or non-local anesthetic drugs were fully reviewed.

Underlying mechanisms of LE treatment

In cases of LAST, the effects of LE treatment can be largely divided into indirect and direct effects; however, because of some overlapping effect, the effects cannot be separated completely. Nevertheless, these two effects appear to contribute synergistically to LE resuscitation for LAST and drug toxicity [5,16]. The mechanisms underlying the indirect and direct effects of LE treatment are described in the following sections.

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Lipid shuttle (LE-induced binding of drug and redistribution)

One indirect effect of LE treatment is a static lipid sink in which the lipid phase created by LE absorbs drugs with high lipid solubility (e.g., log P of bupivacaine = 3.41) from the brain and heart. This effect was commonly used to explain the mechanism of LE in the early history of LE treatment as a rescue antidote [3]. Many physicians continue to believe that lipid sink is the sole underlying mechanism for LE treatment; however, this is not supported by several clinical and laboratory studies. LE treatment using a pharmacokinetic model based on physiological principles has been found to reduce the bupivacaine concentration in the heart and brain by only 11% and 18%, respectively, which is insufficient to explain the phenomenon of LE resuscitation [17]. LE treatment during bupivacaine toxicity using a physiological pharmacokinetic model indicates that bupivacaine accumulation in the muscle affects the survival outcome from bupivacaine toxicity [16]. In addition, LE was not found to have any effect on the concentration of free bupivacaine in human when bupivacaine was administered followed by an infusion of LE or Hartmann's solution [18]. However, LE decreases the context-sensitive half-life of plasma bupivacaine, which is associated with increased redistribution [18]. LE was not found to alter the time to early onset of toxicity in the central nervous system arising from levobupivacaine and ropivacaine administration in humans; however, it reduced the peak plasma concentrations of both levobupivacaine and ropivacaine, suggesting that LE may attenuate rapidly increasing plasma concentrations after extravasation of levobupivacaine and ropivacaine [19]. Additionally, LE was not found to produce any significant differences in the subjective symptoms of the central nervous system or electroencephalographic band power in a randomized controlled clinical study involving lidocaine toxicity in humans [20]. However, it was found to decrease the area under un-entrapped (non-lipid bound) lidocaine–time curves more than Ringer's acetate solution, suggesting that LE administration may lead to an augmented distribution of lidocaine into the tissue through an increased volume of distribution [20].

In the laboratory experiment, while LE does reduce the elimination half-life of bupivacaine and levels of bupivacaine in the brain and heart, it also increases the distribution half-life of bupivacaine and the levels of bupivacaine in the liver, suggesting an LE-induced increase in the clearance of bupivacaine [21]. Additionally, LE reduces bupivacaine content in the frontal lobe and cerebellum and organ-to-blood partitioning of bupivacaine in the heart, frontal lobe, cerebellum, lung, and kidney and increases the concentration in the liver and the decay rate in the heart and cerebellum, suggesting LE-induced scavenging and redistribution of bupivacaine from the brain and heart to the liver [22]. LE administered 30 min after toxicity induced by the intravenous administration of the tricyclic anti-depressant amitriptyline increases the arterial plasma amitriptyline concentration with a concomitant decrease in the brain and reduction in the ratio of the amitriptyline concentration between tissues (the brain and heart) and arterial plasma, suggesting that LE entraps amitriptyline from the brain and heart to the plasma [23]. The extent to which LE was found to reduce local anesthetic concentration in an *in vitro* experiment was found to be positively correlated with lipid solubility of the local anesthetic (bupivacaine [log P = 3.41] > ropivacaine [log P = 2.9] > mepivacaine [log P = 1.95]), suggesting a lipid solubility-dependent sequestration of local anesthetics by LE [24,25]. LE has been found to reverse vasodilation caused by toxic doses of bupivacaine, levobupivacaine, ropivacaine, lidocaine, and mepivacaine in a lipid solubility-dependent manner in isolated rat aortas [26,27]. Furthermore, LE reverses the decreased cell viability caused by toxic doses of bupivacaine more than that caused by toxic doses of mepivacaine, suggesting that the LE-mediated reversal of decreased cell viability is associated with the lipid solubility of local anesthetics [28]. Consistent with previous reports, LE has been found to attenuate hypotension caused by toxic doses of the relatively highly lipid-soluble β-blocker propranolol (log P = 3.48), whereas it has no effect on hypotension caused by the relatively less lipid-soluble β-blocker metoprolol (log P = 2.15), indicating that the LE-mediated blood pressure response may be dependent on the lipid solubility of the offending drug [29,30]. LE also sequesters the highly lipid-soluble anti-arrhythmic drug amiodarone (log P = 7.2) into its lipid phase and improves the reduction in the mean arterial pressure caused by toxic doses of amiodarone, suggesting that LE-mediated sequestration contributes to improved hemodynamic changes [31]. In addition, LE was found to significantly reverse the decreased cell viability induced by toxic doses of the calcium channel blocker verapamil compared to that induced by diltiazem in rat cardiomyoblasts, suggesting that the LE-mediated reversal of decreased cell viability caused by toxic doses of calcium channel blockers depends on the lipid solubility of the drug (log P: verapamil = 3.79 versus diltiazem = 2.8) [32]. LE attenuates the vasodilation induced by the dihydropyridine L-type calcium channel blocker amlodipine (log P = 3), which may be partially associated with amlodipine absorption by LE [33]. LE reverses the impaired myocardial contractility and the reduction in L-type calcium current induced by toxic doses of verapamil with a concomitant decrease in verapamil concentration, thereby supporting the role of the LE-mediated scavenging effect [34].

A previous study analyzing case reports suggested that drugs requiring LE resuscitation in more than two pediatric patients (of

total n = 31) with non-local anesthetic drug toxicity were highly lipid-soluble (log P > 2: lamotrigine = 2.57, amlodipine = 3, propranolol = 3.48, anti-depressant bupropion = 3.6, anti-arrhythmic drug flecainide = 3.78, and amitriptyline = 4.92) [15]. In addition, for drug overdose, the reduction in the areas under the drug plasma concentration–time curve and half-life of the offending drugs resulting from LE treatment may be predicted more accurately using drug capture capacity than log P because log P is a static value that indicates the partitioning of a drug into octanol and water [35]. The capture capacity, mainly determined by log P, reflects the effect of LE on the pharmacokinetics of the offending drug [35].

Taken together, these reports suggest that the "dynamic lipid shuttle (subway)" is currently widely accepted as a mechanism underlying LE treatment [3,36]. According to the dynamic lipid shuttle, LE creates many lipid compartments in the blood, and the lipid phase of LE subsequently absorbs drugs with high lipid solubility (e.g., bupivacaine) from organs receiving high blood flow (the brain and heart), which appears to be dependent on the drug's lipid solubility [36]. LE with highly lipid-soluble drugs (log P > 2) is then delivered to the liver, muscle, and adipose tissue for detoxification and storage [36]. Thus, drugs with a high lipid solubility (log P > 2) may contribute to successful LE resuscitation via the lipid shuttle.

Positive inotropic effect

Another effect of LE treatment is positive inotropic effect. LE treatment alone induces the increase in the maximum rate of left intraventricular pressure increase and decrease and the rate–pressure product, suggesting that LE-induced positive inotropic and lusitropic effects reverse the myocardial depression induced by bupivacaine [37]. In addition, LE alone increases left ventricular systolic pressure by inhibiting nitric oxide (NO) release [38]. Toxicity due to the highly lipid-soluble anesthetic bupivacaine produces QRS widening and QT prolongation due to the blockade of cardiac sodium and potassium channels, leading to myocardial depression [39,40]. Toxic doses of bupivacaine, levobupivacaine, and ropivacaine produce a markedly negative inotropic and lusitropic effect [41]. However, LE increases the time to onset of QRS widening, arrhythmia, and asystole caused by bupivacaine [40]. Local anesthetics in a lipid solubility-dependent pattern inhibit the human-ether-a-go-go-related gene channel of the heart, which codes for the rapid delayed rectifier potassium channels, leading to a prolonged QT interval and torsade de pointes [42]. Bupivacaine toxicity prolongs the QT interval, but LE reduces the Tpeak-to-Tend interval (transmural dispersion) and restores the sinus rhythm [43]. Bupropion, flecainide, amitriptyline, and lamotrigine are highly lipid-soluble, non-local anesthetic medications whose toxicity results in cardiac sodium channel inhibition, myocardial depression, and QRS widening, phenomena similar to the pharmacological properties of bupivacaine [15,39,44]. According to an analysis of case reports, intractable cardiovascular depression caused by toxic doses of the bupropion, flecainide, amitriptyline, and lamotrigine with high lipid solubility was ameliorated by LE treatment [13–15]. Moreover, LE reversed the reduction in left ventricular systolic pressure (+dP/dt) and systolic blood pressure induced by levobupivacaine toxicity in Langendorff-isolated heart preparation [45].

Taken together, these reports suggest that LE provides direct positive inotropic effects to reverse the myocardial depression and QT and QRS prolongation caused by toxic doses of local anesthetics and cardiac sodium channel blockers (amitriptyline, flecainide, bupropion, and lamotrigine), which may be partially mediated by the LE-induced sequestration of highly lipid-soluble drugs. In other words, the lipid shuttle and positive inotropic effects are difficult to separate completely, because they overlap in the LE treatment of LAST. For example, the LE-mediated reversal of decreased myocardial depression caused by a toxic dose of bupivacaine may be mediated by indirect LE-induced sequestration of bupivacaine from the heart (decreased organ-to-blood partitioning of bupivacaine) or a direct inotropic effect of LE.

Supply of fatty acids and attenuation of mitochondrial dysfunction

A third effect of LE treatment is the supply of fatty acids and attenuation of mitochondrial dysfunction. Bupivacaine inhibits carnitine acylcarnitine translocase, which is involved in the transport of long-chain fatty acids to cardiac mitochondria and subsequent ATP production via fatty acid β-oxidation in the cardiac mitochondria [7,9]. LE was found to attenuate the inhibition of carnitine acylcarnitine translocase caused by toxic doses of bupivacaine in rat cardiomyoblasts, and LE alone was found to increase the activity of carnitine acylcarnitine translocase, suggesting that LE may attenuate the inhibition of carnitine acylcarnitine translocase caused by bupivacaine and subsequently reverse impaired ATP production [46]. Pretreatment with ATP nearly reverses bupivacaine-induced myocardial depression [47]. LE attenuates bupivacaine-induced cardiotoxicity by inhibiting oxidative stress and mitochondrial dysfunction [46,48]. Bupivacaine, levobupivacaine, and ropivacaine attenuate mitochondrial ATP production [49,50]. However, LE attenuates the cardiotoxicity caused by bupivacaine, which is mediated by fatty acid oxidation and inhibition of mitochondrial permeability transition pore (MPTP) opening [51]. Furthermore, toxic doses of the anti-malarial drug chloroquine, β-blocker propranolol, and chemotherapeutic agent doxorubicin

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cause cardiotoxicity, which is mediated by mitochondrial dysfunction or decreased ATP production via the generation of reactive oxygen species (ROS) [52–54]. However, LE inhibits the cardiotoxicity caused by these drugs, which is mediated by the mitigation of mitochondrial dysfunction via the attenuation of ROS production [52–54].

Taken together, these reports suggest that LE attenuates the cardiac toxicity induced by toxic doses of bupivacaine, propranolol, chloroquine, and doxorubicin, which is likely mediated by the inhibition of mitochondrial dysfunction via the inhibition of ROS production, fatty acid supply, and ATP production.

Glycogen synthase kinase-3β phosphorylation

A fourth effect of LE treatment is glycogen synthase kinase-3β phosphorylation. Post-ischemic treatment with LE has been found to decrease ischemic reperfusion injury in an in vivo rat experiment by inhibiting MPTP opening, which is mediated by glycogen synthase kinase-3β phosphorylation induced by extracellular signal-regulated kinase or phosphoinositide-3 kinase and Akt [55]. LE was found to attenuate apoptotic cardiac cell death induced by bupivacaine in H9c2 rat cardiomyoblasts via the inhibition of MPTP opening, which is mediated by the phosphoinositide-3 kinase, Akt, and glycogen synthase kinase-3β pathways [56]. In addition, LE treatment inhibits bupivacaine-induced cardiotoxicity via the delta opioid receptor and the phosphorylation of glycogen synthase kinase-3β, which may subsequently lead to the inhibition of MPTP opening and attenuation of ischemic reperfusion injury [57]. Furthermore, LE attenuates the cardiotoxicity caused by verapamil in rat cardiomyoblasts, which is mediated by a pathway involving phosphoinositide-3 kinase, Akt, and the delta opioid receptor [32]. This inhibits toxic doses of amlodipine-induced cardiac toxicity, which is mediated by phosphoinositide-3 kinase and ATP-sensitive potassium channels [58]. The LE-mediated attenuation of cardiotoxicity caused by doxorubicin appears to be mediated partially by glycogen synthase kinase-3β [54].

Taken together, these reports suggest that LE inhibits cardiotoxicity induced by bupivacaine, verapamil, amlodipine, or doxorubicin via the phosphoinositide-3 kinase, Akt, and glycogen synthase kinase-3β pathways, which may contribute to the attenuation of ischemic reperfusion injury via the inhibition of MPTP opening.

Inhibition of NO-induced vasodilation via inhibition of NO release

A fifth effect of LE treatment is the inhibition of NO-induced vasodilation via inhibition of NO release. LE attenuates NO-induced vasodilation by inhibiting NO production [59]. LE alone increases blood pressure and vascular resistance in humans, but reduces vascular compliance and flow-mediated vasodilation [60,61]. The polyunsaturated fatty acid linolenic acid (18:3n-3), which is a long-chain fatty acid contained in Intralipid and Lipofundin MCT/LCT, attenuates NO-mediated vasodilation induced by acetylcholine [62]. In addition, linolenic acid inhibits the vasodilation caused by toxic doses of bupivacaine in endothelium-intact rat aorta, which seems to be mediated by the inhibition of NO release [62].

Levobupivacaine, ropivacaine, and mepivacaine, at toxic doses, cause vasodilation (attenuated vasoconstriction), which is partially mediated by endothelial NO production [63–65]. LE reverses the vasodilation induced by toxic doses of levobupivacaine (3×10^{-4} M), which is partially mediated by the inhibition of endothelial NO synthase (Ser1177) phosphorylation [26,63]. The dihydropyridine L-type calcium channel blocker amlodipine (racemic), which is composed of S-amlodipine and R-amlodipine, induces vasodilation primarily by inhibiting L-type calcium channels (S-amlodipine) and partially releasing endothelial NO (R-amlodipine) [66,67]. Furthermore, methylene blue, a nonspecific inhibitor of guanylate cyclase, improves the reduced mean arterial pressure induced by toxic doses of amlodipine, suggesting that the inhibition of amlodipine-induced NO release by methylene reverses the reduced blood pressure [68].

Taken together, these reports suggest that LE-induced inhibition of NO release contributes to the reversal of severe vasodilation induced by toxic doses of local anesthetics and amlodipine.

LE treatment for LAST and drug toxicity

To treat LAST using LE, the following steps should be followed [2]. The airway should be maintained to prevent hypoxia, hypercarbia, and acidosis, which exacerbate LAST. LE is administered after the airway is established. Seizures are treated with benzodiazepines, LE, or a small amount of succinylcholine to decrease hypoxia and acidosis. Cardiac arrest is treated with a low dose of epinephrine (< 1 μg/kg), amiodarone, LE, and advanced cardiac life support. Cardiopulmonary bypass is used to treat patients who are unresponsive to LE and vasopressors.

Suggested dosing regimen for LE treatment

The recommended LE dosage for systemic toxicity induced by local anesthetics is as follows: an initial bolus administration of intravenous 20% LE at 1.5 ml/kg over 2–3 min followed by a continuous intravenous infusion of 20% LE at 0.25 ml/kg/min [2]. The rate of the continuous infusion of 20% LE is adjusted to 0.5 ml/kg/min for hemodynamically unstable patients [2]. The initial upper recommended LE dose is approximately 12 ml/kg [2]. De-

spite differences in the toxicokinetics induced by local and non-local anesthetics (mainly via oral administration), case reports regarding LE treatment as an adjuvant therapy to treat drug toxicity caused by non-local anesthetic drugs frequently use the recommended LE dosing regimen for LAST [14,15]. However, according to an analysis of case reports, various LE dosing regimens have been used for the treatment of drug toxicity caused by non-local oral anesthetics [14,15]. While LAST is mostly caused by the inadvertent administration of toxic doses of local anesthetics intravenously, non-local anesthetic drug toxicity is mainly associated with oral administration. Thus, the pharmacokinetics of drug toxicity differ. Increased myocardial contractility and scavenging effects are induced by 1% plasma triglycerides in LE, and the maximal clearing capacity (K_1) of Intralipid has been reported to be 110 ± 4 μM/L/min [22,37,38,69]. Considering these previous reports, the recommended dosing schedule for LE treatment as an adjuvant drug in non-local anesthetic drug toxicity, which produces 1% plasma triglyceride, is as follows: an initial intravenous bolus administration of 20% LE at a dosage of 1.5 ml/kg, adjusted to 0.25 ml/kg/min for 3 min, and subsequently adjusted to a continuous infusion at 0.025 ml/kg/min [70]. This dosing regimen can be followed for a maximum of approximately 8.5 and 6.8 h in pediatric and adult patients, respectively, according to the maximum daily recommended dose (pediatrics, 3 g/kg/24 h; adults, 2.5 g/kg/24 h) of 20% Intralipid for nutritional support recommended by the American Academy of Pediatrics and Food and Drug Administration [70,71].

Half-life of LE

The half-life of the triglycerides contained in Intralipid and Lipofundin MCT/LCT, which are composed of 100% long-chain fatty acids alone, and 50% long-chain and 50% medium-chain fatty acids, respectively, have been reported to be 13.7 ± 5.2 and 9 min, respectively [72,73]. The half-life of the triglycerides contained in LE is shorter than that of the local anesthetics (bupivacaine: 4.6 ± 2.6 h and ropivacaine: 2.3 ± 0.8 h) and non-local anesthetic drugs that cause toxicity [72–74]. In particular, the half-life of non-local anesthetic drugs is much longer than that of LE [72,73]. The bupivacaine-induced cardiotoxicity that is initially treated by the administration of Intralipid (150 and 350 ml) recurs 40 min after treatment in the absence of a continuous infusion [75]. This recurrence may be associated with the longer half-life of bupivacaine (4.6 ± 2.6 h) compared with Intralipid (13.7 ± 5.2 min) [72,74,75]. Thus, patients who recover from cardiovascular collapse due to LAST after LE resuscitation should be monitored for at least 4–6 h in the intensive care unit [2]. Additionally, as the half-life of oral amlodipine has been reported to be 36 h [76], the decreased plasma amlodipine concentration by initial LE treatment has been found to re-elevate 24 h after the cessation of Intralipid administration, which may be associated with the unsustained capture of amlodipine by LE because of the very short half-life of the triglycerides contained in Intralipid compared with the plasma half-life of amlodipine [72,76,77]. Additionally, while the plasma concentration of the anti-depressant trazodone initially decreases after the administration of Intralipid, a rebound increase in the plasma trazodone concentration occurs after the cessation of the Intralipid infusion, which may be due to the longer half-life of trazodone (10–12 h) compared with that of triglycerides [72,78–80]. Moreover, although the mental state in patients who have received a toxic dose of the anti-depressant bupropion is improved after the initial Intralipid administration, it is altered after the infusion is discontinued, which may be due to the longer half-life of bupropion (21 ± 9 h) compared with Intralipid [81,82].

Considering the above reports, the half-life of the offending drugs should be considered during LE therapy for toxicity caused by non-local anesthetic drugs. In general, the half-life of the triglycerides in LE is lower than that of the offending drugs [72,73]. Thus, re-elevation of the plasma concentrations of the offending drugs or recurrence of symptoms may occur after discontinuation of LE. Further studies are needed to examine the optimal dosing regimen and timing of LE administration as an adjuvant therapy for drug toxicity caused by non-local anesthetic drugs.

Type of LE

Intralipid contains a high concentration of linoleic acid (18:2n-6, a polyunsaturated essential fatty acid) from soybeans, which increases the production of powerful pro-inflammatory mediators [83,84]. As a result, 20% Lipofundin MCT/LCT with 50% medium-chain fatty acids (from coconut) and 50% long-chain fatty acids (from soybean), 20% SMOFlipid with 30% long-chain fatty acids (from soybean oil), and ClinOleic acid with 20% soybean oil, which is lower than linoleic acid of 20% Intralipid, were developed to reduce lipid peroxidation and pro-inflammatory responses [83,84]. Thus, currently, the availability of Intralipid in hospitals is limited; however, SMOFlipid and ClinOleic, which are used for parenteral nutrition, are comparatively more available. Many studies have reported that Intralipid is most frequently used to treat drug toxicity caused by local or non-local anesthetic drugs [14,15,85]. However, alternative preparations of LE, including Lipofundin MCT/LCT, SMOFlipid, and ClinOleic, can be used for the treatment of urgent and critical cardiovascular depression caused by toxic doses of local or non-local anesthetic drugs [14,15,85,86].

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Positive clinical responses associated with LE treatment for non-local anesthetic drug toxicity

According to an analysis of case reports regarding LE treatment of drug toxicity caused by non-local anesthetic drugs, LE treatment can be used as an adjuvant therapy to reverse hypotension, QT prolongation, and QRS widening; reduce the incidence of comas and seizures; improve the Glasgow Coma Scale score; and decrease the amount of catecholamine and inotropic drugs required for hemodynamic support [13–15]. Symptoms improved by LE therapy in pediatric patients with non-local anesthetic drug toxicity have been reported in the following decreasing frequency: cardiovascular symptoms alone > central nervous symptoms alone > cardiovascular and central nervous symptoms together [15].

Side effects in LE treatment

A relatively small amount of LE is used as a solvent for propofol and etomidate, administered through intravenous bolus injection or continuous infusion; however, the dosage of LE administered for drug toxicity caused by LAST or non-local anesthetic drugs is higher than that used for anesthesia [84]. Accordingly, even if the LE dosing regimen for LAST treatment is well-understood by the anesthesiologist, managing the potential side effects associated with LE can be a challenge without sufficient experience. Most reports on the adverse effects of LE have been derived from the use of LE for total parenteral nutrition rather than for resuscitation. However, the use of LE according to the guidelines for LAST is considered relatively safe compared to the use of LE for long-term total parenteral nutrition, and has a lower risk compared with cardiovascular collapse caused by LAST. Thus, the risks associated with LE treatment as rescue therapy are much manageable. A retrospective study of LE treatment as rescue antidote reported that the side effects include pancreatitis, adult respiratory distress syndrome, and lipemia-induced interference in laboratory examinations (e.g. serum chemistry) ordered after ultracentrifugation is performed [87]. In addition, other direct effects of LE treatment include pyogenic reactions and fat overload, which are rare [88]. Fat overload (fat accumulation) induced by LE can result in hyperlipidemia, seizures, jaundice, decreased platelet count, hemolytic anemia, increased clotting time, and fat embolism [88]. LE used for the treatment of LAST directly causes iatrogenic lipidemic plasma, which leads to interference in several laboratory examinations, including albumin, magnesium, and glucose [89]. Ultracentrifugation is essential for minimizing laboratory errors associated with lipemic interference caused by lipid rescue therapy [89,90]. Large doses (1,500 and 4,200 ml) of LE, which was administered to treat non-local anesthetic drug (herbicide alone or digoxin and alprazolam) toxicity, have been found to cause obstruction of hemofiltration and extracorporeal membrane oxygenation [91,92]. Thus, based on the clinical presentation of patients with drug toxicity, both the benefits and side effects of LE treatment for drug toxicity should be considered.

Further research directions

While significant research regarding LE resuscitation has been conducted, further studies are needed to clarify the following aspects. First, as LE decreases the area under the drug concentration–time curves and the half-life of lipid-soluble drugs, the therapeutic concentration of some lipid-soluble drugs administered for supportive treatment (for example, hemodynamic support) during drug toxicity may be reduced after LE administration [35,93]. Thus, as vasopressors and inotropic drugs, including epinephrine, norepinephrine, phenylephrine, vasopressin, and dopamine, are commonly used for hemodynamic support during drug toxicity, the effects of LE on the blood pressure response evoked by these drugs and their plasma concentrations are undefined. Second, Intralipid with only 100% long-chain triglycerides can sequester bupivacaine 2.5 times more than Medialipid with 50% long-chain and 50% medium-chain triglycerides [24]. In addition, Intralipid-induced attenuation of the cardiac sodium channel blockade by bupivacaine is greater than that induced by Lipofundin MCT/LCT [94]. In contrast, Lipofundin MCT/LCT with 50% long-chain and 50% medium-chain triglycerides, extracts more bupivacaine from human serum than Intralipid [25]. Furthermore, Lipofundin MCT/LCT has been found to reverse vasodilation induced by toxic doses of bupivacaine in isolated rat aorta as well as reverse the decreased cell viability caused by toxic doses of chloroquine more than Intralipid [27,53]. Lipofundin MCT/LCT also inhibits NO-mediated vasodilation by acetylcholine more than Intralipid, suggesting that the medium-chain triglycerides contained in Lipofundin MCT/LCT may have a significant effect on the inhibition of NO-mediated vasodilation [59]. However, in terms of the extent of the reversal of toxic doses of levobupivacaine-induced vasodilation, Intralipid and Lipofundin MCT/LCT are not significantly different [63]. Both Intralipid and Lipofundin MCT/LCT reverse the cardiac electrophysiologic alteration (prolongation of atrioventricular and intraventricular conduction time) induced by bupivacaine, with no significant difference [95]. Thus, further studies are needed to determine which type of triglycerides (long-chain triglycerides or medium-chain triglycerides) is optimal for the treatment of cardiovascular collapse induced by toxic doses of local anesthetics or other drugs. Third, given that negative case reports of LE treatment for toxicity caused

by non-local anesthetics are more difficult to publish than positive case reports, and many analyses examining the outcomes of LE treatment on non-local anesthetic drug toxicity have relatively small sample sizes, similar studies on large cohorts are required for further evaluation of the effects of LE resuscitation on patients with non-local anesthetic drug toxicity. In addition, the physicochemical properties of non-local anesthetic drugs that are strongly correlated with positive responsiveness to LE treatment for non-local anesthetic drug toxicity (besides lipid solubility) remains to be determined. Further studies are required to determine the optimal dosing schedule and timing of LE administration as adjuvant therapy for oral drug toxicity. Fourth, LE alone (i.e., Lipofundin MCT/LCT or Intralipid) has been found to increase intracellular calcium levels in H9c2 rat cardiomyoblasts [96]. In addition, long-chain polyunsaturated fatty acids (linoleic and linolenic acids) increase voltage-dependent calcium channel currents in cardiac myocytes [97]. However, polyunsaturated fatty acids decrease voltage-dependent calcium currents in rat ventricular cardiomyocytes [98]. Additionally, Lipofundin MCT/LCT alone decreases the availability of cardiac sodium channels, leading to a reduction in the opening of L-type calcium channels [94,99], whereas Intralipid alone has no effect on the L-type calcium channel current of ventricular cardiomyocyte [34]. Bupivacaine inhibits cardiac sodium and calcium channels, which alters calcium dynamics, including a reduced peak calcium amplitude in pluripotent stem cell-derived cardiomyocytes [99]. Thus, given that the effect of fatty acids on intracellular calcium levels is controversial, further studies are needed to examine the effect of fatty acids alone and combined treatment with fatty acids and local anesthetics on the intracellular calcium levels in cardiac myocytes.

Conclusion

In conclusion, the underlying mechanisms of LE resuscitation used for the treatment of toxicity caused by local or non-local anesthetic drugs, include the lipid shuttle (LE-mediated binding and enhanced redistribution), positive inotropic effects, fatty acid supply, attenuation of mitochondrial dysfunction, glycogen synthase kinase-3β phosphorylation, and attenuation of NO production. LE administered as an adjuvant drug with supportive treatment may be effective for patients with intractable cardiovascular depression caused by toxic doses of lipid-soluble non-local anesthetic drugs (log P > 2). However, further research is needed to determine the appropriate dosing schedule and optimal timing of LE treatment for toxicity caused by orally-administered non-local anesthetic drugs with high lipid solubility. In addition, the physicochemical properties (besides lipid solubility) that contribute to patients' positive responses to LE treatment as an adjuvant therapy requires further clarification.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

Soo Hee Lee (Conceptualization; Data curation; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing)
Ju-Tae Sohn (Conceptualization; Data curation; Funding acquisition; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing)

ORCID

Soo Hee Lee, https://orcid.org/0000-0002-6047-633X
Ju-Tae Sohn, https://orcid.org/0000-0003-0102-5800

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