Past, Present, and Future of Lipid Resuscitation Therapy

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Abstract
Lipid resuscitation therapy was identified in 1998 as an effective treatment for local anesthetic systemic toxicity in an animal model. Since the original observation, the field has progressed tremendously with successful clinical translation and expansion of use to treatment of other types of drug overdose. Recent work has expanded our understanding of the mechanism of this novel treatment, one that includes both a dynamic scavenging component and direct cardiotonic effect. In this review, we discuss the past, present, and future of lipid resuscitation therapy with a focus on our understanding of the mechanism and directions that the field is moving, both from a clinical and basic research side. (JPEN J Parenter Enteral Nutr. XXXX;xx:xx-xx)

Keywords
Intralipid; lipid emulsion; bupivacaine; toxicity; overdose; local anesthetic

Clinical Relevancy Statement
Drug overdose from both illicit and prescription drugs is a serious health problem and cause of mortality in the United States. Lipid resuscitation therapy (LRT) is used clinically as an antidote for local anesthetic systemic toxicity and nonspecific xenobiotic overdose. This review provides a history of the field, summarizes our understanding of the mechanism of LRT, evaluates the evidence about what drugs are amenable to treatment with LRT, and discusses possible methods to improve LRT.

Part I: Introduction and Overview
Very soon after the commercial release of Intralipid in 1962, scientists and clinicians started to propose the use of intravenous (IV) oil and fat emulsions as drug binders or as components of extracorporeal lipid dialysis. In that same year, Russell and Westfall1 reported that IV corn or cottonseed oil could shorten the duration of thiopental anesthesia. Subsequent to this, in 1965, Shinaberger and colleagues2 demonstrated that adding olive or cottonseed oil to the dialysate could enhance removal of glutethimide, with a report of successful use of lipid extracorporeal hemodialysis on a patient a few years later.3 In the following years, specialized devices for lipid dialysis were developed,4 and proposals of more specially designed dialytes for detoxification were postulated.5 Laboratory investigations demonstrated that the addition of corn oil to dialytes was effective at moving drug out of the plasma and into the dialyte, particularly for imipramine, amitriptyline, methaqualone, and glutethimide.6 Furthermore, in 1974 Kriegstein and colleagues7 were the first to demonstrate that a commercially available fat emulsion (10% Lipofundin, B. Braun, Taguig City, Philippines) could bind chlorpromazine in vitro and save rats from lethal chlorpromazine toxicity in vivo. The field soon went quiet, and the clinical translation of lipid dialysis was not pursued as interest of the community moved to pharmacological interventions for overdose. Then, in 1998, it was demonstrated that pretreating or resuscitating rats with an IV infusion of lipid emulsion (ILE; 20% Intralipid from Baxter Pharmaceuticals, Deerfield, IL) without accompanying dialysis could increase the median lethal dose of IV bupivacaine.8 This initial finding was promising because bupivacaine toxicity can produce an intractable cardiac arrest that was viewed for many years as potentially untreatable.9 These findings were confirmed for a dog model in 2003 with the evidence that after 10 minutes of bupivacaine-induced
hypotension, all dogs given ILE recovered normal vital signs, while all saline-treated controls died.\textsuperscript{10} Findings in both of these models were experimentally interesting, but they did not constitute a clinical breakthrough.

The first clinical translation of LRT was reported in 2 separate cases of local anesthetic systemic toxicity (LAST) in 2006 by Rosenblatt et al\textsuperscript{11} and Litz et al.\textsuperscript{12} Rosenblatt et al described a patient treated with 20 mL bupivacaine and 20 mL mepivacaine for regional anesthetica of the brachial plexus. The patient progressed to seizures and asystole. When the patient did not respond to traditional advanced cardiac life support, 100 mL of 20\% Intralipid was injected, and within seconds, a cardiac rhythm resumed. In a similar scenario, in the case of Litz et al, a woman received 40 mL of 1\% ropivacaine that was followed by seizures and asystole. When epinephrine failed to revive the patient, 100 mL Intralipid was administered by bolus with another 100 mL delivered over the subsequent 10 minutes at 10 mL/min, leading to rapid hemodynamic recovery from toxicity. Following these reports, many more cases were reported with examples of successful resuscitation from overdoses of bupivacaine,\textsuperscript{11,13–25} mepivacaine,\textsuperscript{26,27} ropivacaine,\textsuperscript{12,28–30} and lidocaine.\textsuperscript{15,30,31} Taken together, these observations indicated the successful clinical translation of the original laboratory finding. Within the anesthesia community, the result rapidly changed practice for treatment of LAST, with ILE replacing vasopressors as the first therapy for suspected LAST and fueling recommendations to incorporate lipid infusion from professional organizations.\textsuperscript{32–35}

**Standard Dosing**

In the case of a suspected local anesthetic overdose, the standard recommendation from these professional organizations for LRT is a dose of 1.5 mL/kg lean body mass (~100 mL for an adult) of 20\% lipid emulsion delivered as a bolus over 1 minute followed by a continuous infusion of 0.25 mL/kg/min for at least 10 minutes after return of spontaneous circulation. The bolus could be repeated once or the infusion doubled for continued hypotension, but the total dose, including both bolus and infusion, should not exceed 12 mL/kg (~800–1000 mL for an adult).\textsuperscript{32–35} This keeps the total dose of lipid below the 24-hour limit of 12.5 mL/kg of 20\% lipid emulsion set by the Food and Drug Administration (FDA).

**Local Anesthetic Systemic Toxicity**

Following the clinical translation, LRT has provided an effective treatment option for LAST. However, like many famous treatments, including penicillin and aspirin, the mechanism was not understood at the time of discovery or clinical translation. Even more vexing, we do not fully understand the key mechanisms underlying LAST itself. Like many medicines, local anesthetics are small, amphipathic molecules that, at low concentrations, exert specific effects, but as concentrations increase, they can bind to unintended targets inside the cell and disrupt normal cellular and physiologic homeostasis. Local anesthetics are used clinically to inhibit pain transmission by blocking voltage-gated sodium channels. However, orders of magnitude below their sodium channel blocking threshold,\textsuperscript{36,37} they can interfere with intracellular signaling,\textsuperscript{38} and above their sodium channel blocking threshold, they interfere with mitochondrial metabolism, thereby altering oxidative phosphorylation.\textsuperscript{39} These multiple effects lead to a combination of systemic issues with both vasodilation\textsuperscript{40} and cardiac collapse.\textsuperscript{41} It is still unclear which effect is responsible for the lethality of LAST.\textsuperscript{42} The problem is complex and incompletely understood, and the mechanism of LAST most likely underlies its responsiveness to treatment with LRT.

**Part II: Mechanism of Lipid Emulsion Therapy**

Intertwined into the history of LRT is the progression of ideas about how LRT works to reverse local anesthetic toxicity. The original mechanistic hypothesis proposed by Weinberg and colleagues\textsuperscript{43} in 1998 was that the lipid emulsion could provide a novel compartment for drug to partition into once injected intravenously. This idea became known colloquially as “the lipid sink.” The theory of a partitioning effect comported with early studies of lipid dialysis as a rescue agent.\textsuperscript{1–3} Furthermore, studies by Mazoit and colleagues\textsuperscript{12} also agreed with earlier in vitro binding studies,\textsuperscript{6,7} demonstrating that lipid emulsion would capture drugs based on the drugs’ octanol/water coefficient (LogP). However, more recent studies have elucidated that the full rescue effect of LRT during LAST is multimodal. The mechanism of LRT-based reversal includes both a scavenging effect that removes drug from tissue and a direct-cardiac effect that improves cardiac output once drug is removed from cardiac tissue.\textsuperscript{43} Of note, the cardiotoxic effect only occurs once drug concentrations in cardiac tissue drop below ion channel-blocking thresholds.

**Scavenging Effects**

First, the ILE used during LRT provides a compartment for drugs to partition into, as confirmed by in vitro,\textsuperscript{32,44,45} ex vivo,\textsuperscript{46,47} and in vivo studies.\textsuperscript{43} In vitro studies have also demonstrated that lipid emulsion can accelerate the recovery of channel conductance and facilitate the return of protein signaling systems when delivered to cell and tissue preparations undergoing toxicity.\textsuperscript{48–53} This is true for sodium channels,\textsuperscript{48,49,53} and phenylephrine-dependent vasoconstriction.\textsuperscript{50–52} Based on the in vivo studies, the IV lipid compartments do not permanently sequester the drug but instead accelerate redistribution of drug. Thus, LRT can facilitate recovery while not directly contributing an obvious “sink.”\textsuperscript{54} For local anesthetics such as bupivacaine, this accelerates the movement of drug from drug-susceptible organs, such as the brain and heart, to organs that...
can store (muscle, adipose), detoxify (liver), and excrete (kidney, bladder) the drug. \textsuperscript{43,55} This mechanism of improved redistribution by ILE has also been observed in human models for local anesthetics\textsuperscript{46,57} and amitriptyline.\textsuperscript{58} In both of these cases, the lipid transiently captures drug in the lipid-laden plasma and rapidly moves it to other organs.

Therefore, with our improved understanding of lipid resuscitation, we view lipid as a “shuttle” to move drug around as opposed to a “sink” that captures and isolates drug. Litonius and colleagues\textsuperscript{56} discussed this effect in a human model as a “shortening of the context-sensitive half-life,” while Kazemi and colleagues\textsuperscript{59} termed this as a hypothetical subway instead of sink. This “lipid shuttle” or capture/release mechanism has significant implications on what drugs and situations that lipid can be useful for. In addition, in the case of recovery from toxicity, this accelerated redistribution is a very powerful mechanism but also illustrates the need for continued cardiopulmonary resuscitation efforts, including chest compressions and ventilation.

**Nonscavenging or Direct Cardiac Effects**

Direct benefits of the lipid on cardiac output, independent of the scavenging effects, have been seen in a number of systems. Scavenging effects on their own cannot explain the rapid recovery from LAST,\textsuperscript{60} but the addition of a direct cardiac effect can explain this rapid recovery.\textsuperscript{43,61} These nonscavenging effects improve cardiac output both in the absence of toxicity\textsuperscript{62,63} and during toxicity,\textsuperscript{43} confirming the suspicion that lipid emulsions such as Intralipid can provide direct physiological effects on the heart or vasculature.\textsuperscript{64} In vitro comparisons of the effect of LRT on different local anesthetics have also demonstrated the presence of direct effects on a cellular level. Despite the issue that the LogP of mepivacaine makes it less susceptible to scavenging by binding, studies by Wagner et al\textsuperscript{48} demonstrated that lipid has a direct effect on cardiomyocytes in vitro that were also exposed to mepivacaine. The improved cardiac output improves the blood pressure, which is often a concern with local anesthetic toxicity. In addition, it continues to facilitate the accelerated redistribution.

The underlying cause of improved cardiac output via lipid emulsion is unclear but remains an interesting basic science question. The volume of ILE is a definite component, but the other contributors are unclear.\textsuperscript{61} Many ideas have been proposed, most of which lack convincing scientific evidence or have too many experimental confounders. The 2 most popular hypotheses are “the calcium hypothesis” and “fatty acid hypothesis.” Gueret et al\textsuperscript{65} proposed the calcium hypothesis in an editorial, claiming that fatty acids increase Ca\textsuperscript{2+} influx into cardiac myocytes to produce inotropy. They cited a single article from 1992 in support of the idea that used guinea pig ventricles.\textsuperscript{66} Many others have repeated this calcium hypothesis without providing experimental data. However, many subsequent studies (some from the same group that performed the 1992 study) have demonstrated that fatty acids inhibit calcium influx in more suitable animal models.\textsuperscript{67-72} Therefore, based on the experimental literature, this hypothesis is unlikely. A second hypothesis is an assertion that the mass action of lipid emulsion can overcome the block in fatty acid processing that bupivacaine causes.\textsuperscript{39} This hypothesis is also unlikely because cardiac output does not recover until drug concentrations in the myocardium drop below the thresholds for blockade of mitochondrial function.\textsuperscript{43} Other ideas have been proposed, but many have significant methodological issues related to the local anesthetic insult. Inhibitor studies are problematic because the lipid can sequester the inhibitor-compound in addition to the drug of interest (most often bupivacaine). In addition, local anesthetics, including bupivacaine, lidocaine,\textsuperscript{39} and cocaine,\textsuperscript{73} block fatty acid processing in the mitochondria, which produces an ischemic-like injury. Thus, the combinatorial toxicity of other agents (especially agents that exacerbate ischemic injury) with bupivacaine makes results uninterpretable without appropriate controls. A few studies have pointed to fatty acid processing and compounds used in ischemia-reperfusion injury as inhibiting the direct effects of lipid, but most failed to account for the potential combinatorial effects with bupivacaine. As such, their contribution to the mechanism of LRT is very hard to infer. Finally, there is evidence that the vasoconstrictive properties of Intralipid in the vasculature play a role, but the relative contributions of cardiac versus vascular aspects are unclear.\textsuperscript{74}

**Future Mechanistic Directions**

There are a number of questions left to answer about the mechanism with regard to both the scavenging component and the direct effects. It is not entirely clear whether LogP is the only predictor of the scavenging effect. As with other drugs, partitioning can occur due to a combination of lipophilicity (LogP) and pH.\textsuperscript{75,76} As such, other factors may contribute to partitioning by Intralipid that could explain how Intralipid effectively treats overdoses from less lipophilic drugs.\textsuperscript{77,78} In addition, the characteristics and evolution of the IV scavenging effect of Intralipid are incompletely described. A better understanding of it could help aid optimal dosing or inform on next-generation therapies. With regard to the direct cardiac effects, there is still a lot to understand. The primary theories of calcium influx and mass action have little evidence to support them. Alternative theories have been proposed that involve the vasculature,\textsuperscript{74} channel-specific effects,\textsuperscript{48} fatty acid processing,\textsuperscript{80} intracellular signaling,\textsuperscript{81} and mitochondria.\textsuperscript{41,82} One or more of these systems is likely involved, but the exact mechanisms are still a matter of speculation.

**Part III: Clinical Future**

While local anesthetics provide a good model to investigate the mechanism of LRT, the larger clinical future use of LRT as a treatment lies outside of the realm of local anesthetics. Clinically significant LAST occurs at a rate of roughly 1 out of 1000 nerve blocks, and while precise numbers are not available,
cardiovascular collapse with LAST is an infrequent event. This rate will hopefully decline as improved awareness and methodologies such as ultrasound guidance are adopted.\textsuperscript{53,54} Prescription drug overdoses are still a major cause of death in the United States, outpacing car accidents, suicide, and sepsis in the past 10 years.\textsuperscript{85–87} Therefore, it was an important step when Dr Archie Sirianni saved a patient from a bupropion and lamotrigine overdose using LRT in 2008,\textsuperscript{88} opening the door to use of LRT as an antidote to an important public health problem.

Even with this transition to a more general antidote, the clinical future of ILE is undefined. Recommendations from professional societies are modified versions of local anesthetic recommendations,\textsuperscript{34} even though the pharmacokinetics of nonlocal anesthetic overdoses are clearly very different from those in local anesthetic overdose. In particular, local anesthetic overdoses are parenteral in nature, with direct injection of drug into the vasculature or relatively rapid absorption from a tissue depot. In contrast, nonlocal anesthetic overdoses are most often enteral in nature due to either intentional or accidental ingestion of a prescription medication. These differences will necessitate different treatment strategies, which are currently being defined.\textsuperscript{73}

Without a broader base of clinical research to draw on, insight into the usefulness of lipid for different toxicities comes to us either from basic science studies or clinical case reports. A number of articles have compiled and evaluated the use of lipid in human clinical situations, all coming to similar conclusions.\textsuperscript{99–96} For both local anesthetic and nonlocal anesthetic overdoses, only low-level evidence, comprising largely animal models and case reports, exists in support of using LRT. Beyond case reports, a clinical registry demonstrated an improvement in Glasgow coma scale (GCS) and blood pressure associated with use of ILE.\textsuperscript{93} A randomized clinical trial from Iran of treatment of nonlocal anesthetic overdose found the same effect of improvement in GCS in patients treated with lipid relative to those untreated.\textsuperscript{94} All these retrospective analyses have come to the conclusion that the evidence is strongest for the treatment of LAST, but evidence for treating toxicity aside from LAST is less compelling. Recently, a working group was formed by the American Academy of Clinical Toxicologists with the explicit purpose of providing guidelines for the use of LRT in both local anesthetic and overdose from other drugs based on the available evidence.\textsuperscript{95} While it is obvious that robust clinical trials are needed for nonlocal anesthetic toxicity (with appropriate dosing and timing), in the interim, lipid will remain as a “Lazarus” measure for many overdoses.

In the following section, we address the evidence for efficacy of LRT beyond treating local anesthetics and the questions that need to be answered to move LRT forward as a general antidote.

Cocaine

As one of the most widely used recreational drugs, cocaine overdose is a problem that has not been adequately addressed insofar as there are no specific antidotes, and treatment is largely supportive.\textsuperscript{96} Cocaine is a potent local anesthetic, and therefore it is reasonable to infer that it might be amenable to ILE treatment given that it has similar physicochemical properties as other local anesthetics and that its toxicity is based on similar mechanisms of action. Two case reports describe the successful treatment of cocaine toxicity with ILE;\textsuperscript{97,98} and 2 basic science studies demonstrate the effectiveness of ILE in animal models of cocaine overdose.\textsuperscript{99,100} Furthermore, lipid also reverses the cardiac depression caused by the both cocaine and cocaethylene, a by-product of coadministration of ethanol and cocaine.\textsuperscript{100} As cocaine is primarily ingested parenterally, either by smoking or absorption through mucus membranes, the parenteral nature of the overdose makes its treatment with LRT more similar to that for LAST.

Other Illicit Drugs

Heroin and opiates cause the most drug-related deaths in the United States, but as there exists a specific, highly effective receptor antagonist, there is very little relevance of lipid to these overdoses.\textsuperscript{101} Two categories of illicit drugs that might benefit from lipid infusion are the synthetic cathinones, commonly referred to as “bath salts,” and both synthetic and natural cannabinoids,\textsuperscript{102} both of which are lipophilic. Of the cathinones, α-pyrrolidinopentiophenone has a LogP of 3.65 and 3,4-methylenedioxypyrovalerone has a LogP of 3.06. Of the cannabinoids, tetrahydrocannabinol has a LogP of 7.68. Furthermore, lipid has already been used to treat marijuana intoxication in dogs.\textsuperscript{103}

Antianxiety and Sleep Aids

GABAergic medications that function as antianxiety or sleep aids are the most prominent cause of drug-related emergency room visits. These are often treated with supportive care. In addition, the GABAergic antagonist, flumazenil, is reported to aid in treatment of these overdoses but is used infrequently,\textsuperscript{104} potentially due to concerns about seizures or other complications.\textsuperscript{105} A very limited number of case reports have described treatment of overdoses in this group with LRT, including clonazepam,\textsuperscript{106} diazepam,\textsuperscript{107} and zolpidem/ alprazolam.\textsuperscript{108} However, all of these reports were presentations of multidrug overdose. No animal models exist for benzodiazepine overdose treated with LRT, and coupled with the lack of case reports, it is impossible to assess potential effectiveness of Intralipid for antianxiety agents. However, since they comprise such a significant cause of drug-related emergency department (ED) admissions, lipid or liposomes for benzodiazepine toxicity should be studied more. As an over-the-counter sleep aid and motion sickness medication, diphenhydramine also poses the risk of overdose. A few recent reports have identified that lipid is apparently beneficial in diphenhydramine overdose.\textsuperscript{109–111}
Antidepressants and Antipsychotics

The first case of nonlocal anesthetic toxicity that was treated with lipid was a case of combined lamotrigine and bupropion overdose.88 Many antidepressant or antipsychotic medications make sense as treatment targets with ILE because of the lipophilicity needed to cross the blood-brain barrier and because of their structural similarity to local anesthetics. Since the first case report, a significant number of other toxicities have been treated with LRT, including amitriptyline,111–117 quetiapine,106,114 lamotrigine,78,79,88,114 bupropion,88,118–120 and doxepin.121 Rabbit models have demonstrated the effectiveness of lipid as a treatment for IV clomipramine toxicity.122–124 Furthermore, in pig studies, lipid is shown to entrap amitriptyline into the plasma,58 complying with the scavenging theory.

However, there have also been negative results. A number of pig studies have demonstrated no beneficial effect of ILE on amitriptyline overdose,125,126 but interpretation of these results is problematic because pigs have a systemic hypersensitivity reaction to Intralipid, leading to pulmonary hypertension and arterial oxygen desaturation.127–130 In a similar study in rats with oral amitriptyline overdose, ILE reduced survival compared with other groups, potentially due to the different route of administration.131 We discuss the question of oral overdoses in the section “Part IV: Next-Generation Lipid Therapy.”

Antidepressants and antipsychotics were among the drugs treated in the registry study93 and a preliminary clinical trial of lipid in nonlocal anesthetic overdose.94 Based on the positive results in case reports, animal models, clinical reviews, and registry reports, it seems that both antidepressants and antipsychotics hold potential as targets for scavenging therapy. Additional work should be promoted to better understand dosing and to identify specific scenarios where lipid may provide benefit.

Cardiac Medications

Another group of drugs that pose a risk of overdose, particularly in elderly populations, are cardiac medications, especially ß-blockers and the calcium channel blockers. Overdoses with ß-blockers, propranolol108,132–134 and metoprolol107,114,135,136 have been treated with LRT. However, animal studies have not demonstrated similarly promising results. These studies demonstrate that Intralipid may be beneficial in more lipophilic ß-blocker toxicity, providing benefit for propranolol-induced hypotension in rabbits137 and rats138 and some benefit in atenolol toxicity139 but no benefit to blood pressure in metoprolol toxicity.140 Furthermore, in the case of propranolol-induced hypotension, Intralipid was not as effective as insulin/glucose for ameliorating toxicity in rabbits.141 Mechanically, we know that adrenergic signaling can interfere with LRT,142 and it is possible that ß-blockers as well as adrenergic agonists will produce some interference with the positive effects of ILE as adrenergic sensitization is one of the theories of lipid-induced vasoconstriction.143

In contrast, the results for treatment of calcium channel blocker toxicity have been more promising. Many case reports have asserted the usefulness of LRT for calcium channel blocker overdose, including verapamil90,93,144–149 diltiazem93,150–153 and amlodipine140,154–156 overdose. Furthermore, in experimental settings, ILE has benefited animals with IV verapamil toxicity.157–159 However, in a rat model of oral overdose, supplementation of lipid made toxicity worse, potentially by pulling drug into the vascular space.131 How optimal treatment of oral overdoses might differ from that for parenteral (read, local anesthetic or cocaine) overdose is a clinically relevant and complex issue.

Veterinary Overdoses

Outside of human medicine, LRT has provided significant benefit for poisoned animals. A number of other reviews have covered the use of ILE in veterinary medicine.160–162 In particular, Intralipid has been used extensively to treat ivermectin77,163–166 and permethrin167–170 toxicity. In particular, Peacock et al171 conducted a randomized trial of lipid emulsion in permethrin toxicosis in felines and found a robust rescue effect of the lipid emulsion in comparison to saline. Beyond that, a number of other overdoses with potential translational relevance have been reported as effectively managed with ILE, including moxidectin,172 ibuprofen,173 carbamazepine,106,119 and baclofen.106 Baclofen is interesting in particular because it is nonlipophilic and may serve as a good model of how lipid can be used to treat nonlipophilic drug overdose. Finally, ILE has been used to treat marijuana intoxication in dogs.103 This is also of interest because of the increase in marijuana overdose following its legalization for medical and recreational purposes.102

Herbicide Overdose

The weed killer glyphosate has the potential for serious complications in humans following intentional or accidental exposure, and LRT has been reported to alleviate toxicity in patients.174 The possibility that Intralipid could provide benefit for herbicide toxicity like glyphosate certainly warrants further study.175

Clinical Trial

Beyond a greater understanding of the mechanism, the greatest challenge in LRT is designing a clinical trial to test the clinical efficacy compared with other standard treatments. Currently, the treatment algorithm for drug overdose is a grab-bag of medications, including multiple pressors, sodium bicarbonate, high-dose insulin, methylene blue, and LRT, the latter often only given when all other options are exhausted. In the case of calcium channel blocker overdose, none of these treatment options has evidence beyond low-level animal models and case reports to support the usage.176 Even high-dose insulin lacks clinical trials to support its use. As such, most antidotes for drug overdose are assessed by animal studies, case reports,
physician experience/preference, and expert opinion. In the case of local anesthetics, we know that high-dose epinephrine can interfere with the effectiveness of ILE\textsuperscript{177} and that vasopressors are less effective at treating overdose in animal models.\textsuperscript{178}

As such, treatment algorithms for LAST recommend the use of LRT before vasopressors. However, the same is not known for other drugs, and extrapolating from animal models of LAST is questionable. Before progressing to trials, a better understanding of dosing and timing for LRT in oral overdose is needed, along with a better understanding of which specific drugs might be amenable to treatment. Of possible drug candidates, we support continued investigation of drugs with greater basic science and case study validation, including calcium channel blockers, bupropion, tricyclic antidepressants, and cocaine.

**Part IV: Next-Generation Lipid Therapy**

As we move to a better understanding of the mechanisms of LRT and parse out the separate effects contributed by the scavenging and the direct cardiotonic mechanisms (as well as other possible effects), we can begin to design next-generation agents for the treatment of drug toxicity. The following section discusses some of the questions in the future of LRT.

**Optimizing Treatment for Oral Overdoses**

The pharmacokinetics of oral overdose are fundamentally different from those of IV or parenteral toxicity and therefore require a different dosing of LRT. Oral overdose will lead to prolonged adsorption of drug from the gastrointestinal (GI) tract. A number of animal models have demonstrated that lipid could be less effective in treating oral overdose.\textsuperscript{151} Harvey et al\textsuperscript{179} raised the possibility that early treatment with lipid in oral overdoses could accelerate toxicity. As the mechanism of lipid is partially driven by redistribution, this effect could theoretically increase the rate of absorption of a lipophilic drug from the GI tract and movement to sites of toxicity before movement to sites for storage and detoxification. Since oral overdose remains a significant issue, there is a pressing need to understand how ILE will modify the pharmacokinetics and drug parameters of an oral overdose. Furthermore, there is a need to determine how timing and dosing of ILE will change based on type of drug.\textsuperscript{73}

**Refinement of Dosing/Delivery Recommendations**

As part of the oral overdose question, there is a broader question about optimal dosing. We know that lipid provides a dose-dependent response, with 30% Intralipid accelerating the speed of recovery relative to 20% ILE in an animal model of bupivacaine overdose.\textsuperscript{61} Higher percentage formulations (>$40\%$) break down due to instability, but a higher dosage such as 30% might function as a better clinical antidote than the current clinical standard of 20%. Furthermore, there are questions about the bolus volume and the rate of a subsequent infusion. Dosing will differ based on intoxication route as we have discussed with regard to oral overdoses, but there are other considerations. We need a better understanding of the pharmacokinetics and pharmacodynamics of drug-induced toxicity and how different infusion paradigms might modify these pharmacokinetics for a given drug. We might then be able to optimize and simplify the dosing recommendations. Finally, we know the lipid is effective when delivered via the intraosseous space, and this may change treatment options in high-risk or battlefield overdose situations, but further research is needed.\textsuperscript{180} As mentioned earlier, a working group has been developed to provide recommendations for use of LRT in both local anesthetic and non–local anesthetic toxicity.\textsuperscript{95} Standardization of use is a worthy goal for current usage parameters of LRT as a “Lazarus” measure with bolus + infusion derived from LAST treatment recommendations. However, current guidelines outside of LAST are almost certainly nonoptimal and may be far from optimal based on new mechanistic insight.\textsuperscript{43,73} Better dosing and timing recommendations are needed. These should be determined in basic models and ultimately tested in randomized trials for the highest quality of evidence.

**Better Scavengers**

The drug delivery community is interested in developing next-generation drug scavenging agents,\textsuperscript{181,182} and one expects that reverse engineering of the principles underlying drug delivery will yield effective and efficient scavengers. Intralipid was not originally designed as a drug binding agent, and it is likely that other agents with higher binding capacities and greater specificity could be developed. Some assert that the major binding capacity in Intralipid comes from the phospholipids used to emulsify the soybean oil. If this is the case, then increasing the amount of phospholipids could increase the lipophilic binding capacity and provide a greater drug-capturing potential. Alternatively, different properties such as surface charge could be used to more effectively scavenge charged agents. In particular, pH-gradient liposomes are already studied experimentally as capture agents\textsuperscript{183–185} because of their widely studied properties as drug delivery agents.\textsuperscript{186,187} Other, next-generation strategies for drug scavenging have been developed,\textsuperscript{185,188–190} and they hold significant promise for the future and potential clinical use. Two recent reviews have discussed in more depth the current field of liposomal scavenging systems and the possibilities they hold.\textsuperscript{191,192} One major advantage of liposomal delivery systems is their ability to hold drug. This property differentiates them from LRT, which captures and releases drug to facilitate accelerated redistribution. In some cases, the pure capture may improve recovery relative to Intralipid, but in other cases, the capture/release mechanism might be preferred. Liposomes hold much promise, but there are many practical and regulatory hurdles before they become clinical tools.
Combinatorial Therapy

Alternatively, combinatorial binding schemes could be considered in future detoxification scenarios. Many other binding agents have been proposed for treatment of toxicity and could be used alone or in combination with ILEs. Cyclodextrins have been used for reversal of drug toxicity or as a binding agent for cocaine, even though they are not as effective at reversing cocaine toxicity as Intralipid. Additional work is needed to refine these agents or combinations.

Since ILE exerts scavenging-independent effects, any advance in LRT must improve on both the scavenging and non-scavenging components of LRT. As an example, liposomes have been compared in animal models with traditional ILEs but do not produce the same level of recovery. A number of agents are currently used to provide cardiotoxic effects during overdose and could be used to supplement pure binding agents. High-dose insulin is used extensively for calcium channel blocker overdose, and the combination of ILE and high-dose insulin has been used together effectively. Insulin and lipid coadministration in animal models does not seem to produce synergistic effects because they may activate overlapping metabolic rescue pathways. However, there does not seem to be a contraindication to giving them concurrently as insulin has shown benefit in some circumstances, and LRT has been shown better in others. Another alternative is methylene blue, which will increase the median survival time for calcium channel blocker toxicity by increasing pulse rate and mean arterial pressure. Other reviews have covered the topic well, with the conclusion that 1–2 mg/kg of 1% methylene blue can be beneficial in toxin-induced shock as an adjuvant to vasopressors.

Lipid as a Dialysis Agent

Finally, we return to the beginning. One of the more exciting recent developments is the suggestion that lipid or optimized liposomes could be used as an intraperitoneal dialysis agent. Intralipid was examined as a dialysis agent for an animal model of clomipramine toxicity, with the combination of ILE and plasma exchange providing the greatest benefit. Furthermore, Forster and colleagues have developed a novel liposomal formulation that may offer more optimized peritoneal capture properties. The use of lipid as a hemodialysis or peritoneal dialysis agent could provide benefit in the case of extended toxicity such as oral overdose of a drug with an extremely long pharmacokinetic half-life. However, the clinical usefulness of such ideas remains to be seen with many experimental, clinical, and regulatory hurdles to address.

Part V: Conclusion and Future Directions

LRT has progressed significantly since the demonstration of its efficacy in the rat and dog models of severe, local anesthetic overdose. In the past few years, our understanding of the mechanism has evolved substantially, with recovery being driven by a combination of a “lipid shuttle” and a direct cardiotoxic effect, both of which accelerate redistribution of the toxin. Furthermore, the development of next-generation agents is progressing with hope for clinical translation in the near future. For now, there is much work left to do. We still need to assess what drugs are most amenable to treatment with LRT, determine optimal dosing parameters for oral overdoses, and implement a randomized, controlled clinical study to test and compare effectiveness with other treatments. The latter is of great need as only low-level evidence exists for treatment. In the interim, we recommend further research on reversing toxicity of drugs that pose significant clinical problems and have higher likelihood of success of treatment by ILE. Examples of these include tricyclics, bupropion, calcium channel blockers, and cocaine. In particular, the method of gaining greatest benefit from LRT in treating an oral overdose needs to be addressed. As part of this question, optimal dosing and timing need to be determined since the current treatment paradigm used in parenteral overdoses could likely be modified with improved results specifically for oral intoxications. The field is full of exciting questions to answer, and progress will lead to lives saved since drug toxicity remains a significant problem worldwide.

Statement of Authorship

M. R. Fettiplace and G. Weinberg contributed to the conception and design of the research; M. R. Fettiplace drafted the manuscript; and M. R. Fettiplace and G. Weinberg agree to be fully accountable for ensuring the integrity and accuracy of the manuscript. Both authors read and approved the final manuscript.

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