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REVIEWS

REVIEW OF THE PHARMACOLOGICAL DATA ON INTRAVENOUS LIPID EMULSIONS

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ABSTRACT

INTRODUCTION: Initially, the clinical application of lipid emulsions (LEs) was parenteral nutrition. Since 2006, LEs have been widely used as an antidote for various intoxications with lipophilic drugs. Despite the widespread use of LEs, there is insufficient information regarding their pharmacokinetics and mechanism of antidote action. That is why detailed knowledge of their pharmacokinetic parameters and complex mechanism of action is particularly important.

AIM: The aim of the study is to make a detailed literature analysis of the pharmacokinetics and of all putative mechanisms of antidote action of LEs.

MATERIALS AND METHODS: Over 100 literature sources were studied in various databases, including PubMed, ScienceDirect, Research Gate, Google Scholar, and others. These include clinical cases (over 40), laboratory animal experiments (over 20), and medical guidelines and protocols (over 30).

RESULTS: Lipid emulsions have good absorption and 100% bioavailability after intravenous administration. They do not bind to plasma proteins. Lipid emulsions undergo hepatic metabolism similar to chylomicrons. Their plasma half-life is ±10 minutes. The osmolarity of LEs is 270-345 mosm/l. Lipid emulsions cross the blood-brain barrier but do not cross the placental barrier. They are mainly removed from skeletal muscles (47%), splanchnic organs (25%), myocardium (14%) and subcutaneous tissue (13%). LD_{50} in rats is 67.72 mL/kg and in dogs 135 mL/kg. The maximum single harmless dose for a person (70 kg) is 4000–7000 mL/24 h. The most widely advocated mechanism of non-antidote action of LEs is the lipid uptake phenomenon.

CONCLUSION: Evidence collected from numerous clinical cases and laboratory experiments shows high efficiency and great therapeutic safety. Lipid emulsions are distinguished by their ability to dissolve and absorb lipophilic xenobiotics. In the blood, LEs prevent their binding to target receptors or, through the concentration gradient, extract them from critical organs, such as the brain and heart. Lipid emulsions have a cardioprotective effect as energy donors for the myocardium. They also exhibit vasoconstriction, which is important for overcoming toxic shock. Therefore, LEs represent an important therapeutic tool in the fight against intoxications with lipophilic drugs, such as anesthetics, psychopharmacology, and cardiovascular drugs.

Keywords: *ADME, acute drug intoxication, mechanism of action, pharmacology, pharmacokinetics, lipid emulsion*

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INTRODUCTION

The new but increasingly entering clinical toxicology successful treatment with intravenous lipid emulsions (LEs) as a non-specific antidote for fat-soluble toxins is the subject of increasing interest. Initially, the clinical application of LEs was in the field of parenteral nutrition as a source of nutrients and calories for people who are unable to take food per os, as well as in patients with essential fatty acid deficiency. Administered as an individual infusion or combined with other parenteral nutrition, the essential fatty acids provided by LEs are vital for cells and metabolism.

The composition of LEs is key to their therapeutic properties. The most important components of LE are soybean oil, egg phospholipids, and glycerol. Newer generations contain olive and fish oil and are an important source of the essential fatty acids omega-3, 6, and 9.

Soybean oil is a major component of most LEs available on the market. The beneficial properties of soybean oil were known in ancient China as early as 2,000 years ago. The average content of fatty acids in soybean oil in percentages is 51–57% linolenic acid; 23–29% oleic acid; 4.5–7.3% stearic acid; 2.5–6% palmitic acid; 0.9–2.5% arachidonic acid (eicosanoic acid); up to 0.1% hexadecenoic acid; 0.1–0.4% myristic acid. The high content of vitamin E in soybean oil acts as a powerful antioxidant that stimulates the immune system and helps eliminate free radicals. Phospholipids, which are contained in soybean oil, are extremely important for cell differentiation, proliferation and regeneration, as well as for the transport of molecules through cell membranes. Phospholipids play a role in the activity and activation of various enzymes such as Na/K-adenosine triphosphatase, lipoprotein lipase, cytochrome oxidase and receptors (e.g. insulin and others) that have important functions in cellular processes.

Lipid emulsions with the following concentrations are used—10%, 20%, and 30%, and the 20% LEs are most often applied. 10% LE contains 100 g of lipids per 1000 mL, 20% LE contains 200 g of lipids per 1000 mL, 30% LE contains 300 g of lipids per 1000 mL. One gram of lipids corresponds to 5 mL of Intralipid 20%—the most commonly used LE.

Lipid emulsions provide 30% to 50% of non-nitrogenous caloric needs or about 20% to 30% of total calories or 9 kcal/g of energy. The caloric value of LEs varies depending on their concentration. 10% LE provides 1.1 kcal/mL, respectively 20% 2 kcal/mL and 30%—3 kcal/mL. Intralipid 20% provides 2 kcal/mL (1).

The beginning of the use of LEs as an antidote began in 2006 when Rosenblatt published the first report of successful resuscitation with LE after mepivacaine and bupivacaine overdose and the development of life-threatening local anesthetic systemic toxicity syndrome (LAST). After receiving a bolus of 100 mL of 20% LE Intralipid, within 20 minutes the patient's vital signs were restored. Since then, LEs have also been widely used as an antidote for various intoxications with lipophilic drugs such as local anesthetics, antidepressants, neuroleptics, and cardiovascular drugs (2).

Resuscitation protocols include a bolus intravenous dose of 1.5 mL/kg LE over one minute, followed by a continuous intravenous infusion of 0.25 mL/kg/min over 20–60 min (15 mL/kg over 60 min) until circulation is restored (3).

Despite the widespread use of LEs in clinical practice, their pharmacokinetics and pharmacodynamics are not fully understood, especially regarding their antidote characteristics.

AIM

The aim of the present study is to make a detailed literature analysis of the pharmacokinetics and all supposed mechanisms of antidote action of LEs.

MATERIAL AND METHODS

Over 100 literature sources were studied in various databases including PubMed, ScienceDirect, Research Gate and Google Scholar. These include clinical cases (over 40), laboratory animal experiments (over 20), and medical guidelines and protocols (over 30).

RESULTS AND DISCUSSION

1. Pharmacokinetics of LE/ADME

◈ **Absorption**

Lipid emulsions have good absorption after intravenous administration and achieve 100% bioavailability. Their absorption may be increased in

postoperative conditions and after trauma, and decreased in patients with renal failure or hypertriglyceridemia (4).

Lipids in emulsions are presented as nano-dispersed particles rich in triglycerides and stabilized by phospholipids. Triglycerides are usually based on vegetable oils—soybean or fish oil, with a concentration of 10 to 30% (5). Lipid emulsions have a low osmolarity (20% LE: 270–345 mosm/L), thanks to which they can be infused through a peripheral venous route.

◈ **Distribution**

After infusion, LEs exist in the blood in the form of emulsified lipid droplets or multilamellar vesicles. The US Pharmacopeial Convention has established standards to ensure the uniform nature of all LEs, thus limiting the likelihood of venous occlusion associated with parenteral administration, namely that the mean diameter of fat droplets be less than 500 nm regardless of the concentration (6).

Lipid emulsions do not bind to plasma proteins and have biological properties similar to those of chylomicrons. They are structurally similar to chylomicrons but do not have cholesterol esters or apolipoproteins in their composition. The plasma half-life ($T_{½}$) of LEs is ±10 minutes (7).

◈ **Metabolism**

The infused fat particles are cleared from the bloodstream in a manner thought to be comparable to the clearing of chylomicrons. In the circulation, chylomicron-like LEs rich in triglycerides and phospholipids would acquire apolipoproteins (apoC-II and apoE) from the lipoprotein complexes containing them (HDL, VLDL) (8). They could also exchange triglycerides for cholesterol esters via a specific transfer protein with cholesterol ester-containing lipoprotein complexes (HDL and LDL). Acquired apoC-II would activate lipoprotein lipase (LPL), an enzyme attached to the endothelium of capillary vessels. Lipoprotein lipase would break down some of the triglycerides in LE to free fatty acids and glycerol, which would be taken up by adjacent tissues. A small fraction of the free acids would remain in the circulation, binding to albumin. After the action of LPL and the hydrolysis of triglycerides, the size of the lipid particles would decrease, converting them into residual particles that contain mostly cholesterol esters. By means of acquired apolipoproteins—ligands for different types of receptors (including LDL-receptors), residual lipid particles would be utilized not only by the liver, but also by extrahepatic tissues. Thus, LEs can deliver polyunsaturated fatty acids and fat-soluble vitamins to various tissues, including heart muscle whose resuscitation is of particular importance in the rescue of intoxicated patients.

The metabolism of the released fatty acids consists of absorption, oxidation, and esterification. There are two sources of fatty acids for myocardial metabolism:

1. circulating albumin-bound fatty acids derived from adipose tissue by lipolysis;
2. freed from triglyceride-rich lipoproteins from the liver.

Fatty acids enter cardiomyocytes by simple diffusion and by transport through three different membrane fatty acid transporters:

a. fatty acid translocase (FAT)/CD36;
b. fatty acid transport protein (FATP1/6);
c. plasma membrane fatty acid binding protein (FABPpm).

After uptake by the sarcolemma, intracellular fatty acids are activated to form fatty acyl-CoA, which can undergo beta-oxidation or esterification to form intracellular triglycerides. Fatty acid oxidation requires the entry of fatty acyl-CoA into mitochondria, which is dependent on the activity of carnitine palmitoyl transferase (CPT-1).

After translocation into mitochondria, fatty acyl-CoA can undergo beta-oxidation to form acetyl-CoA and subsequent production of ATP by oxidative phosphorylation in mitochondria.

Under physiological conditions, 70–90% of the fatty acids that enter cardiomyocytes are oxidized to generate ATP, while 10–30% are converted to triglycerides mainly through the glycerol phosphate pathway of *de novo* glycerolipid synthesis, involving sequential acyltransferase and phosphatase reactions at the mitochondrial and SR/ER membrane.

Fatty acids are necessary for the maintenance of energy metabolism, cell structure and regulation of cellular processes in the heart muscle, which supports cardiomyocyte regeneration through several mechanisms:

- *Energy maintenance*: The heart muscle is a highly metabolic organ that requires a significant amount of energy for its function. Fatty acids are one of the heart muscle's main energy sources. They are broken down in the mitochondria of cardiomyocytes by a process of beta-oxidation and provide ATP, the main energy source for cells. Adequate provision of energy from fatty acids supports cardiomyocyte functionality and recovery after damage.
- *Synthesis of cellular components*: Fatty acids are essential building blocks for the synthesis of membranes and other cellular components. Cardiomyocyte regeneration requires active cell division and growth, which includes the synthesis of new cell membranes and organelles. Fatty acids are necessary for the synthesis of new membranes and for the maintenance of the overall structure of cells.
- *Signaling molecules*: Some fatty acids and their metabolites can function as signaling molecules and participate in the regulation of cellular processes, including cardiomyocyte regeneration. For example, unsaturated fatty acids, such as omega-3 and omega-6 fatty acids, bind to specific receptors and activate signaling pathways that can influence cell proliferation, apoptosis, and repair.

In the event of energy expenditure, cellular triglycerides can be hydrolyzed as a source of endogenous fatty acids, accounting for 10% of total fatty acid utilization in the heart (9).

- **Elimination**

The rate of elimination of LEs is determined by the composition of fat particles, the nutritional and clinical status of the patient, and the rate of infusion. Intralipid is eliminated from circulation by a metabolic pathway similar to that of endogenous chylomicrons.

There are differences in LE excretion. 20% LE is preferred over 10% LE due to its better clearance as a result of its lower phospholipid content.

Kaijser et al. (1975) demonstrated rapid removal of Intralipid from the blood. He found that the elimination constant (K2) in men is 6.09+0.4%/minute, and in women—7.15+0.33%/minute (10).

The elimination of fat from the bloodstream after intravenous administration has been studied in dogs, rabbits and humans by determining the plasma triglyceride content. The percentage of LE elimination depends mainly on the speed of blood flow in these vessels. Significant amounts of Intralipid are removed from skeletal muscle (47%), splanchnic organs (25%), myocardium (14%), and subcutaneous tissue (13%). In healthy subjects, the maximum rate of clearance of Intralipid in the fasting state is equivalent to 3.8±1.5 g of triglycerides per kilogram of body weight in 24 hours (i.e., 19 mL±1.5 mL lipid substance obtained in 24 hours).

Both the rate of elimination and the rate of oxidation depend on the clinical condition of the patient. Elimination is accelerated in post-operative conditions and after trauma (4).

- **Passing through the blood-brain and placental barrier**

Lipid emulsions are thought to cross the blood-brain barrier. A study by Kayipmaz et al. (2014, 2017) described changes in the central nervous system (CNS) in an experiment with animals treated with an overdose of the lipophilic agent methyl parathion and administered LE. The authors described a reduced expansion of glial cell outgrowths after LE treatment, suggesting protection of the blood-brain barrier and therefore its passage. In addition, increased excitability was observed among LE-treated animals. Animals treated with LE were found to have reduced damage to the brain, liver and pancreas compared to animals treated with standard antidotes alone (11,12).

Currently, there is not enough information regarding the passage of LEs through the placental barrier or the entry into breast milk. Stammers et al. (1995) studied the passage of Inralipid across the placental barrier in pregnant rabbits. Elevated levels of triglycerides and phospholipids have been found only in maternal plasma (13).

- **Acute toxicity of lipid emulsions**

Hiller et al. (2010) studied the median lethal dose (LD_{50}) of LE in rats. For 30 min, rats were treated with 20% LE at doses of 20, 40, 60, and 80 mL/kg, and the control group received saline at doses of 60 or 80 mL/kg. According to the results, the maximum probability of LD_{50} in rats is 67.72 mL/kg (14).

LD_{50} by intravenous infusion in dogs is 135 mL/kg (=13.5 g fat/kg). Animals tolerate a single dose of more than 100 mL of Intralipid 10% per kilogram of body weight, which means that the LD_{50} is more than 10 g fat/kg (14). If these data are transferred to a person, it means that a patient weighing 70 kg receives about 50–4,690 mL in 24 hours up to a maximum single safe dose of 7000 mL/24h (2).

In the Clinic of Toxicology at the Naval Hospital in Varna, LEs were administered to 49 patients (4.45%) of a total of 1100 patients in a dose of 1000 mL/24 h without observed toxic effects (15).

◈ **Subacute toxicity of lipid emulsions**

The subacute toxicity of LEs has also been determined experimentally. The highest intravenous dose of LE studied in rabbits was 4.6 g fat/kg. Even at doses of 180 mL Intralipid 10%/kg/day and 60 mL Intralipid 30%/kg/day, the animals tolerated LE well. No clinical symptoms of toxicity were observed. Apart from a slight effect on general behavior, no other toxic symptoms were noted. Blood and histological analysis were without noticeable deviations from normal values.

Histological analysis revealed no significant damage in the visceral tissues, except for mild to moderate accumulation of lipids in the centrilobular area of the liver, which was believed to be temporary and a result of the high dose of LE used (4).

In our previous study, we analyzed the biochemical and histological changes in rats treated with Verapamil overdose and treated with LE and proved that even doses of 10 mL/kg 20% Intralipid were completely safe in terms of the liver, kidney function and lipid profile ($P<0.05$) (16).

Pharmacological data for LE are summarized in Table. 1.

Table 1. Pharmacological data for LE.

Parameter	Value
Bioavailability	100%
Plasma half-life ($T_{1/2}$)	±10 minutes
Binding to plasma proteins	No
Osmolarity	270–345 mosm/L
Passing through the blood-brain barrier	Yes
Passing through the placental barrier	Weakly
Metabolism	Chylomicron-like hepatic metabolism
Elimination	Skeletal muscle (47%), splanchic organs (25%), myocardium (14%) and subcutaneous tissue (13%). In healthy subjects, the maximum rate of clearance of Intralipid in fasting state is equivalent to 3.8±1.5 g of triglycerides per kilogram of body weight in 24 hours (i.e., 19 mL±1.5 mL lipid substance obtained in 24 hours). One gram of triglycerides corresponds to 5 mL of Intralipid 20%.
	LD_{50} in rats is 67.72 mL/kg. LD_{50} in dogs is 135 mL/kg. Human (70 kg) safety single dose for 24 hours: up to 7000 mL.

Supposed Mechanisms of Antidote Action of LE

◈ **Mechanism of „lipid sink“**

The study of the antidote properties of LEs begins with their application to control LAST. Weinberg (2003) first hypothesized the mechanism of action of LE as an antidote, known as the phenomenon of „lipid sink“. This is currently the most widely accepted mechanism of the antidote action of LE. According to Weinberg, rapid administration of the lipid solution in the circulation creates a lipid phase that engulfs lipophilic xenobiotics and prevents them from binding to target receptors. A concentration gradient is created, which favors the passage of the toxic nox from the tissues of the aqueous phase of the plasma to the lipid phase. The existing concentration

gradient allows toxins to be rapidly removed from areas of high accumulation (brain, heart) (17).

The solubility of long-acting local anesthetics in lipids and the high binding capacity of LE explain their clinical efficacy in cases of LAST.

Emulsified fat droplets form a lipid compartment into which lipophilic substances are theoretically distributed (creating a higher concentration in the lipid compartment) when they flow into an aqueous medium such as blood (where the concentration remains low). The lipid emulsion causes local anesthetics to move away from the heart or brain (high-concentration target organs) into the blood and is retained by the „lipid sink".

By drawing the molecules from the tissues to the lipid part of the blood and keeping them there, the molecules remain less in the aqueous part of the blood, so the concentration gradient becomes greater because there is a relatively higher concentration in the tissues and a relatively lower concentration in the aqueous part of the blood. The gradient created attracts even more molecules from the tissues. The total amount of molecules in the blood plasma increases, but is covered by the lipid fraction. Thus, the concentration of the lipophilic toxic agent decreases in the tissues, which explains the organ protective effect of LEs.

In 2003, Weinberg et al. (2003) investigated the efficacy of LE in anesthetized dogs after intravenous bupivacaine (10 mg/kg) overdose. Resuscitation for this bupivacaine overdose included direct cardiac massage with or without 20% lipid infusion. All dogs that received LE recovered normal blood pressure and ECG, whereas all control animals died (17).

In subsequent experiments using the isolated heart to model bupivacaine-induced toxicity, Weinberg et al. (2006) showed that LE infusion accelerated the clearance of radiolabeled bupivacaine from myocardial tissue compared with controls (18). This experiment confirms the eliciting role of LE.

- **Metabolic influence by increasing the content of intracellular fatty acids and overcoming the reduced production of adenosine triphosphate (ATP)**

In LAST, LEs could theoretically increase intracellular fatty acid content and therefore overcome the reduced ATP production that results from local anesthetic-blocked fatty acid transport and oxidation. It is possible that the resulting increased content of intracellular fatty acids contributes to the improvement of ATP synthesis in cardiomyocytes. In some studies, the cardioprotective effect of LE is manifested through the improvement of energy metabolism in cardiomyocytes.Van de Velde et al. (1996) used a dog model to show that an infusion of 20% LE improved myocardial contractility due to improved fatty acid oxidation (19). Another study conducted by Eledjam et al. (1989) showed that preincubation with ATP in isolated myocardial tissue prevented bupivacaine-induced cardiac depression (20). Therefore, LE infusion may increase the intracellular fatty acid content sufficiently to overcome the reduced ATP synthesis in the myocardium.

The cardioprotective effect and the high efficiency of LEs as an antidote was also confirmed in 49 patients with severe drug intoxications who passed the Clinic of Toxicology at the Naval Hospital in Varna, treated with LE in addition to standard therapy. Mortality in patients treated with LE was 2.29 times lower (4.85%) than those treated without LE—11.1% (216 patients) ($P < 0.05$) (21).

- **By releasing the translocase enzyme inhibited by local anesthetics, improving fatty acid oxidation and ATP delivery to myocardial cells**

One of the most important cardiac proteins with enzymatic characteristics is carnitine-acylcarnitine translocase. It is important for local anesthetics because the heart is a predilection site for fatty acids, ketones, and lactate. Translocase contributes to the passage of acyl-CoA components of long-chain fatty acids across mitochondrial membranes to the site of their oxidation. The transfer of fatty acids with long hydrocarbon chains across the inner mitochondrial membrane occurs with the help of the low molecular weight transporter carnitine. The transfer is carried out by means of a shuttle mechanism.

Carnitine exists in two forms—L- and D-form, with the L-form being the physiologically active. L-carnitine is the only amino acid closely related to fat metabolism ("the fat-burning amino acid"). It prevents the accumulation of lactic acid in the muscle cells. The average amount of L-carnitine in the human body is about 20–25 g, 95% of which is in skeletal muscles. As a structure, L-carnitine was discov-

ered in 1905. Russian scientists Gulevich and Klinberg extracted it from red meat, and this is the reason why they named it carnitine (*from Latin carnis—flesh, meat*).

If translocase is inhibited by local anesthetics, then fatty acids will not be fully oxidized, and the supply of cardiac ATP will stop. This may explain why cardiovascular collapse is so lethal and refractory to conventional treatment (22).

◈ **Through calcium ions**

Fatty acids are known to increase calcium levels in cardiomyocytes. Lipid emulsion infusion can directly increase calcium levels in cardiomyocytes and lead to a direct positive inotropic effect due to the vasoconstriction that occurs, which is able to overcome the toxic shock (23).

◈ **Through alpha-adrenoceptors —vasoconstriction**

Lipid emulsions lead to vasoconstriction. The hemodynamic effects of LEs may be mediated by alpha-1 adrenoceptors. Alpha-1 adrenoceptors are G-protein-coupled receptors whose activation mediates vasoconstriction (24). In the cell, receptor activation stimulates the activity of phospholipase C, which then activates protein kinase C via the phosphoinositol pathway (25).

For example, oleic acid, which is one of the main components of Intralipid, can directly activate protein kinase C, which would lead to vasoconstriction, and in a clinical aspect, it would be relevant to overcome shock in LAST (26).

Lipid emulsions lead to the inhibition of vasodilation. In addition to the effects of protein kinase C, oleic acid and palmitic acid, other components of Intralipid, can inhibit the activation of endothelial NO-synthase (eNOS) and thus block its vasodilatory effects independent of the activation of protein kinase C. Therefore, Intralipid can directly induce vasoconstriction and prevent vasodilatory nitric oxide formation (27).

Lipid emulsions increase the peripheral resistance of the vessels. Intralipid contains small amounts of arachidonic acid, with which linoleic acid interacts. Metabolism of arachidonic acid by cyclooxygenase-1 and cytochrome P450 produces several vasoactive metabolites that partially account for the increased peripheral resistance. (28,29).

All the supposed mechanisms of the antidote action of LE are summarized in Fig. 1.

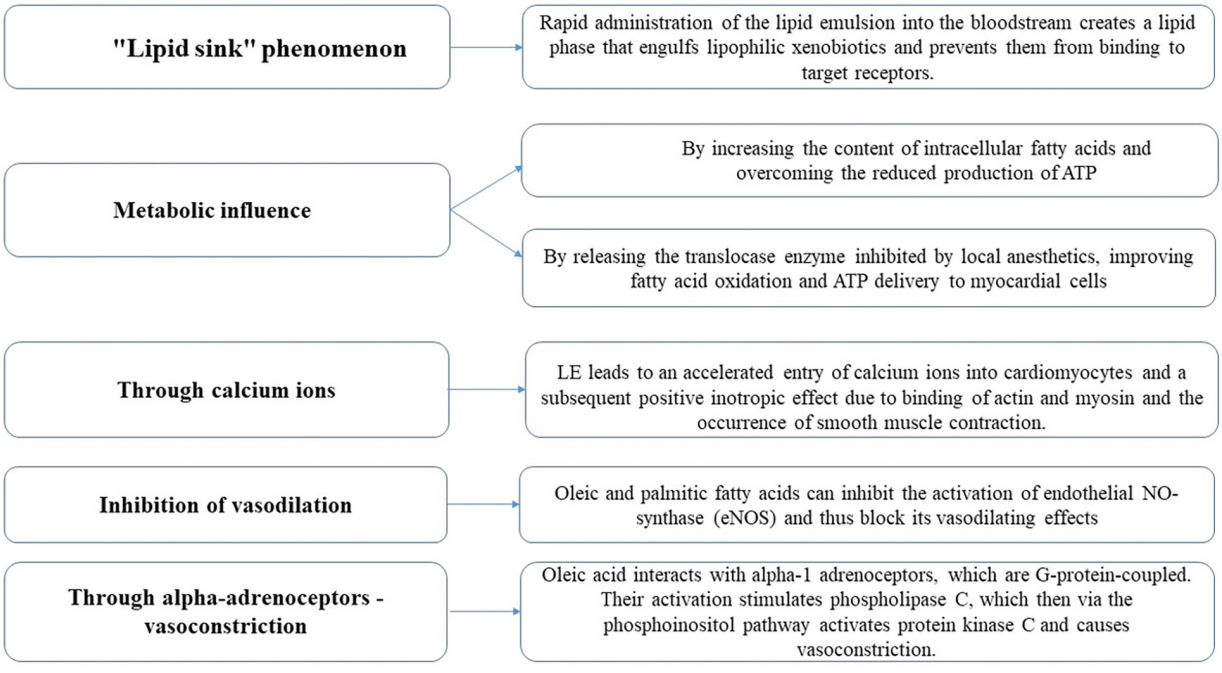

Fig. 1. Supposed mechanisms of the antidote action of LE.

CONCLUSION

The importance of LE as a parenteral food and as an antidote in toxicology and resuscitation clinics is growing. That is why detailed knowledge of their pharmacokinetic parameters and complex mechanism of action is of particular importance. Evidence collected from numerous clinical cases and laboratory experiments shows high efficiency and great therapeutic safety. Lipid emulsions are distinguished by their ability to dissolve and absorb lipophilic xenobiotics. In the blood, LEs prevent their binding to target receptors or, through the concentration gradient, extract them from critical organs such as the brain and heart. Lipid emulsions have a cardioprotective effect as energy donors for the myocardium. They also exhibit vasoconstriction, which is important for overcoming toxic shock. Therefore, LEs represent an important therapeutic tool in the fight against intoxications with lipophilic drugs, such as anesthetics, psychopharmacology, and cardiovascular drugs.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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