Revista Española de Anestesiología y Reanimación 69 (2022) 421–432

Revista Española de Anestesiología y Reanimación

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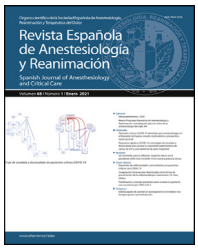

REVIEW

Lipid emulsions in the treatment of intoxications by local anesthesics and other drugs. Review of mechanisms of action and recommendations for use☆

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Received 13 October 2020; accepted 25 March 2021
Available online 20 July 2022

KEYWORDS
Intravenous lipid emulsions;
Local anesthetic toxicity;
Non-local anesthetic toxics

Abstract Intravenous lipid emulsions (ILEs) have been used widely for the treatment of local anesthetic (LA) poisoning and have been proposed as a treatment for intoxication by other drugs. However, the degree of evidence for this kind of therapy is not strong, as it comes mostly from clinical cases.

The aim of this narrative review is to describe the proposed mechanisms of action for ILEs in poisoning by LA and other drugs and to evaluate recent studies in animals that support the recommendations for their use and the experience in humans that support the use of ILESs in both LA and other drug poisoning. For this purpose, a search was performed in the Embase, Medline and Google Scholar databases covering relevant articles over the last 10 years.

In the case of AL poisoning, we recommend applying the protocols dictated by international guidelines, knowing that the degree of evidence is not very high. In poisoning by other drugs, ILEs are recommended in serious situations induced by liposoluble xenobiotics that do not respond to standard treatment.

PALABRAS CLAVE
Emulsiones lipídicas intravenosas;
Toxicidad por anestésicos locales;
Tóxicos no-anestésicos

Emulsiones lipídicas en la intoxicación por anestésicos locales y otros fármacos. Revisión sobre mecanismos de acción y recomendaciones de uso

Resumen Las emulsiones lipídicas intravenosas (ELI) se han utilizado ampliamente para el tratamiento de la intoxicación por anestésicos locales (AL) y se han propuesto como tratamiento de la intoxicación por otros fármacos. Sin embargo, el grado de evidencia de este tipo de terapias no es sólido, ya que proviene en su mayoría de casos clínicos.

☆ Please cite this article as: García-Ramos S, Fernandez I, Zaballos M. Emulsiones lipídicas en la intoxicación por anestésicos locales y otros fármacos. Revisión sobre mecanismos de acción y recomendaciones de uso. Rev Esp Anestesiol Reanim. 2022;69:421–432.

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El objetivo de esta revisión narrativa es describir los mecanismos de acción propuestos para las ELI en la intoxicación por AL y otros fármacos, y evaluar los estudios recientes realizados en animales que sustentan las recomendaciones de su uso y la experiencia en humanos que apoyan el empleo de las ELI tanto en la intoxicación por AL como por otros fármacos. Para ello, se llevó a cabo una búsqueda en las bases de datos Embase, Medline, Cochrane y Google Scholar abarcando los artículos relevantes durante los últimos 10 años.

En caso de intoxicación por AL, se recomienda aplicar los protocolos dictados por las guías internacionales, sabiendo que el grado de evidencia no es muy elevado. En la intoxicación por otros fármacos, las ELI están aconsejadas en situaciones graves inducidas por xenobióticos liposolubles que no responden al tratamiento estándar.

Introduction

In 1998, Weinberg et al.[1] described the therapeutic value of intravenous lipid emulsions (ILE) in the treatment of local anaesthetic systemic toxicity (LAST) in an animal model. Years later, in 2006, the first case report of successful treatment of severe bupivacaine toxicity with ILE was published[2]. Since then, dozens of case reports have been published, accompanied by extensive experimental research in which ILEs have been used in the treatment of bupivacaine and other LA toxicity.

Various scientific societies, especially the American Society of Regional Anesthesia (ASRA), have come out in favour of the use of ILE in LA toxicity. In 2001, at the first ASRA Conference on Local Anesthetic Toxicity, ILE was suggested as a possible treatment for LA toxicity based on existing laboratory and animal experimentation data. Subsequently, in 2008, a new panel of experts met to discuss the issue, and in 2010 the second ASRA Practice Advisory on Local Anesthetic Systemic Toxicity was published, which included the definitive use of ILE in the protocol[3].

This type of antidote is now recommended by all anaesthesia scientific societies for the treatment of LA-induced systemic toxicity[4–6].

Its mechanism of action is considered to be multimodal, insofar as it includes effects that go beyond the commonly accepted lipid sink mechanism[7–10], according to which the lipid emulsion reduces the toxic effect of LA by sequestering its lipophilic molecule. Based on this theory, ILE has also been proposed as a treatment for toxicity by other substances or lipid-based toxins.

The aim of this article is to review the known mechanisms of action of ILEs, the evidence supporting their use in the reversal of LA toxicity, their efficacy in the treatment of toxicity by other substances, and finally, the uncertainties regarding their use.

Material and method

The leading databases (Pubmed, Embase, Cochrane and Google Scholar) were searched for articles in English and Spanish published between 1998 and August 2020. The keywords and terms used for the search were: lipid emulsion, toxicity, local anesthesic toxicity, intralipid, fat emulsions y toxics, toxicology. The terms were used both individually and combined with the *and* operator. We also tracked citations retrieved from the articles selected in the first search. Clinical trials, animal studies, meta-analyses, clinical practice guidelines, and case series were included.

Mechanism of action of lipid emulsions

Although not fully understood, various evidence-based theories have been put forward to explain this mechanism of action.

The scavenging and shuttle mechanism

The most widely accepted explanation for the mechanism of action of ILEs has for many years been the lipid sink effect, whereby these emulsions act as an äbsorbing molecule'' that sequesters the LA and diverts it from critical organs such as the heart and brain. This means that ILEs do not act an antidote for a particular LA, but are instead considered a non-specific treatment based on physicochemical principles. Other theories involving dynamic mechanisms, such as scavenging and shuttle, have now been added to this ''static'' mechanism. According to this hypothesis, the ELI sequesters and transports bupivacaine molecules and other toxins from organs susceptible to toxicity and redistributes them to other organs where the drug is stored (muscle, adipose tissue) and detoxified (mainly the liver)[11,12]. This is due to[10] the capacity of the lipid molecule to bind to different drugs, and the capacity of the emulsion to redistribute the drug.

Binding of the drug to the lipid molecule

The most commonly used lipid emulsion in our setting is Intralipid® 20% (Fresenius-Kabi, Barcelona, Spain), Other types of lipid emulsions are also used to treat LA toxicity, and all are considered valid provided they have a vegetable oil concentration of 20%, since this has been

Table 1 Types of lipid emulsions used in various studies.

	intralipid®	Clinoleic®	Lipofundin®	Structolipid®	Ivelip®	Liposyn® III	Nutrilipid®
Soy oil; g/l	20	4	10	12.8	20	20	20
Olive oil; g/l	—	16	—	—	—	—	—
Coconut oil; g/l	—	—	10	7.2	—	—	—
Egg phospholipids; g/l	1.2	1.2	1.2	1.2	1.2	2.5	1.2
Glycerol; g/L	2.5	2.25	2.5	2.2	2.5	2.5	2.5
Sodium oleate; g/l	—	0.03	—	—	0.03	—	0.03
Percentage of long chain FA	100	100	50	50	100	100	100
Percentage of medium chain FA			50	50			

The different types of ILE used in LA toxicity are shown. Note that all of them contain 20% vegetable oil (mass percentage in grams).
FA: fatty acids; ILE: intravenous lipid emulsions; LA: local anaesthetics.

defined as standard in the international guidelines[13]. Table 1 lists the different types of lipid emulsions used in different studies.

Intralipid® mainly contains purified soybean oil and other excipients, particular egg-yolk phospholipids. The emulsion presents phospholipids in the form of unilamellar vesicles, micelles and clusters of sterols with a hydrophobic core.

Micelles are spherical clusters of phospholipids with a hydrophobic (nonpolar) core and a hydrophilic (polar, negatively charged) surface. This arrangement allows LAs, which are weak bases with both an ionized and un-ionized form, to bind to the nonpolar core of the micelle and also the negatively charged hydrophilic surface. However, the main mechanism is thought to involve binding to the nonpolar, hydrophobic portion of the micelle (Fig. 1). Therefore, the more lipid the drug, the more effective the ILE. ILEs are more effective at reversing the toxicity of more lipophilic LAs such as bupivacaine compared with other less lipophilic LAs such as ropivacaine or mepivacaine[11,12].

LAs, which acts as weak bases at physiological pH, are ionized with a positive charge, and therefore also have affinity for the negative charge of the phospholipids that make up commercial lipid emulsions. As mentioned above, this is not the main mechanism, but should nevertheless be taken into consideration.

Redistribution mechanism

After an accidental intravenous injection, LA spreads first to tissues that receive the greatest blood supply (brain and heart), which are also the key organs where they will develop their maximum toxicity. Studies have shown that ILEs not only sequester the toxic molecule (the lipid sink effect), but also facilitate its redistribution by actively transporting it to other organs (particularly fat, muscle and liver), and in so doing reduce tissue concentration of the toxin in the brain and heart (scavenging and shuttle effects) (Fig. 2). In fact, in healthy volunteers, lipid emulsions reduced the context-sensitive half-life of total bupivacaine plasma concentration by approximately 40%[14].

Other, non-scavenging, benefits of lipid emulsions

Cardiovascular effects

Although the main mechanism of action of lipid emulsions has been described above, they are known to have other benefits that go beyond inducing changes in the pharmacokinetic parameters of toxic substances. ILE emulsions have been shown to have intrinsic cardiovascular effects.

1 *At the cardiac level*, ILEs produce inotropic and lusitropic effects in the heart by different mechanisms. First, being fluids with a direct effect on cardiac preload, they increase contractility according to the Frank-Starling law. Second, the heart uses the fatty acids in lipid emulsions as a source of energy[15,16]. Some authors have also suggested the ILEs act on calcium channels[15] and various enzyme cascades, thus increasing cardiac contractility[17].
2 *At the vascular level*, ILEs increase the fatty acid content of plasma and induces peripheral vasoconstriction, which increases blood pressure in both healthy individuals and patients with acute toxicity. Some authors have hypothesised that this mechanism is related to nitric oxide metabolism disturbances[16] or to changes in sympathetic nervous system activity[18,19].

Postconditioning

Finally, there is evidence to show that ILE administration reduces ischaemia-reperfusion injury[20,21]. Different mechanisms have been suggested, including inhibition of proapoptotic signalling in cells[17] and ischaemia-reperfusion-induced reduction of reactive oxygen species[22]. This is why administration of an ILE could improve prognosis after a serious toxicity-related cardiovascular event.

Current evidence on ILEs in local anaesthetic toxicity

Although most hospitals now include ILEs as the standard of care for severe LA toxicity, and most anaesthesiologists administer them in clinical practice, the evidence for

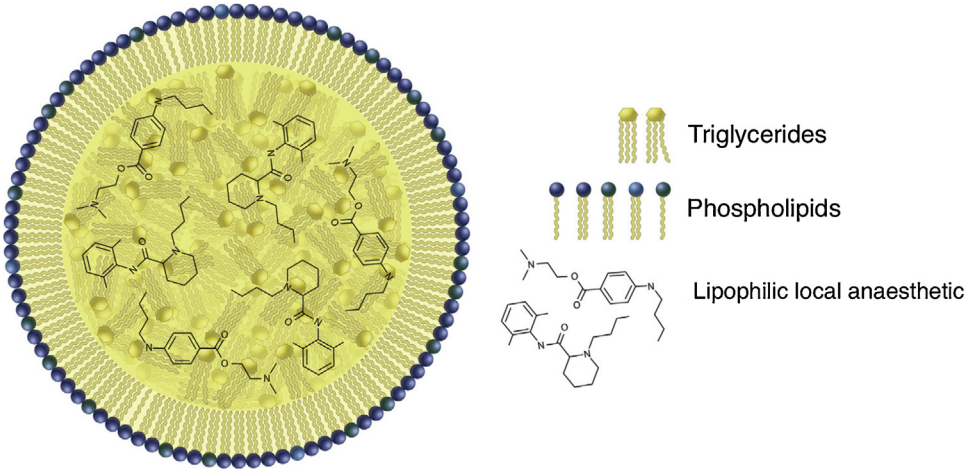

Figure 1 The lipid sink effect. The diagram shows a micelle formed by phospholipids from lipid emulsion. The micelle encloses the different types of triglycerides found in the lipid emulsion, and the local anaesthetic molecules dissolved the triglycerides.

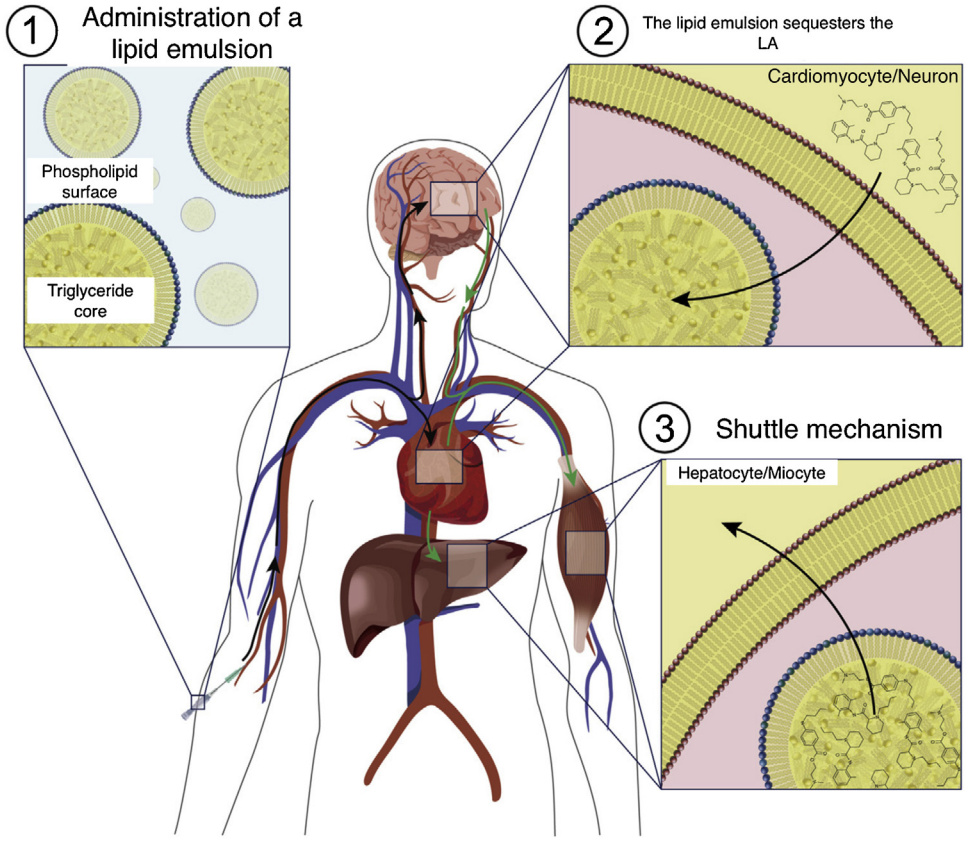

Figure 2 The shuttle mechanism. The lipid emulsion is administered intravenously (1). It first reaches the most widely perfused areas (heart and brain), where it sequesters the toxic local anaesthetic molecules (2). It then redistributes these molecules to other areas of the body, including the liver, where they are metabolized (3).

their use is not as solid as might be expected[23,24], and is mainly derived from experimental studies in animals and cases reports in which publication bias cannot be ruled out.

Regarding experimental studies, a recent meta-analysis of data from 26 clinical studies in different types of animals showed that ILEs were useful in the treatment of LA toxicity[25]. However, after re-analysing these studies, the Lipid Emulsion Therapy Workgroup of the American Academy of Clinical Toxicology (AACT) found little evidence to support the use of ILEs in this context[23].

It is also important to evaluate what the clinical guidelines published by scientific societies have to say about the use of ILE. An analysis of these guidelines shows that although many agree on the core indications, they differ on certain details:

1 The 2015 guidelines of the European Resuscitation Council (ERC)[26] recommend using ILEs in cardiac arrest (caused by any type of local anaesthetic) in combination with standard advanced life support (ALS) measures. They also mention that the use of adrenaline in these cases is controversial.
2 In the American Heart Association (AHA) guidelines[27], administration of ILEs in patients with bupivacaine-related premonitory neurotoxicity or cardiac arrest (together with standard resuscitative care) is a class IIb recommendation. In the case patients with other forms of drug toxicity, ILEs may be administered when standard resuscitative measures have failed (IIb). This is interesting, as it shows that most of the evidence for the efficacy of ILEs is derived from bupivacaine toxicity, and less so from other LAs.
3 After evaluating the current evidence, the AACT Lipid Emulsion Workgroup[23], in consensus with a group of experts, issued the following recommendations for ILE use:
   a For management of cardiac arrest secondary to bupivacaine toxicity, ILE should be used after advanced life support has started *(strong recommendation, low level of evidence)*
   b In cardiac arrest associated with other LAs, the recommendation is neutral (again, different recommendations are described depending on the LA involved)
   c In the case of severe toxicity without cardiac arrest, the group recommends using ILEs to treat bupivacaine toxicity in combination with other treatment modalities *(weak recommendation, low level of evidence)*
   d In case of severe toxicity without cardiac arrest, the group recommends using ILEs in toxicity due to other LAs when other measures have failed. *(weak recommendation, low level of evidence)*
   e In the case of non-life-threatening toxicity, the recommendation to use ILE is neutral.
4 The 2017 guidelines of the American Society of Regional Anesthesia (ASRA)[28] recommend administering ILEs at the first sign of LAST, once the airway has been secured *(strong recommendation, medium level of evidence)*.

This recommendation is based on the observation that ILEs are more effective at the onset of toxicity and have few side effects, so early administration would appear to be reasonable. The ASRA calls for the widespread use of ILEs, while the recommendations of the aforementioned scientific societies are more guarded.

5 In its 2010 clinical guidelines, the Association of Anaesthetists of Great Britain & Ireland (AAGBI)[29] also recommends using ILEs in any situation involving administration of a toxic or intravascular dose of LA.

Despite many case reports and experimental studies in animal models, the evidence supporting ILE administration is weak, and in some cases even contradictory. This has led to discrepancies in the literature, with some authors arguing for and others against administration of ILEs[24,30].

Use of lipid emulsions in non-LA-induced toxicity

Since the first case report describing the successful use of ILE in a patient with LA toxicity[2], attempts have been made to use this strategy in other types of toxicity. The shuttle mechanism put forward by Fettiplace et al.[10] suggests that drugs and toxins with similar pharmacokinetic characteristics to LAs, particularly bupivacaine, might be susceptible to treatment with ILEs.

Theoretically, the main characteristic required by such a toxicant is a lipophilic profile. Any lipophilic drug should have an affinity for fatty emulsions and bind to them, after which the toxicant is transported (shuttled) from sensitive organs to organs such as the liver, where its toxicity is reduced.

The parameter most widely used to measure the lipophilicity of a substance and thus compare this quality between different molecules is the octanol/water partition coefficient, expressed as a logarithm (logP), which is a measure of a substance's hydrophilicity (affinity to octonal) against its lipophilicity (affinity to water).

The higher the coefficient of a given substance, the greater its lipophilicity. Therefore, substances with a logP value greater than 2[31] are considered lipophilic, and toxicity induced by these drugs can be treated by ILEs[32].

This theory is supported by case reports of toxicity due to substances of very diverse chemical composition, such as tricyclic antidepressants, calcium antagonists, sodium channel antagonists, ß-blockers and, to a lesser extent, other drugs such as antimalarials (chloroquine) and other antiparasitics (ivermectin)[33].

in vitro studies have shown that the addition of lipid emulsion 20% significantly reduces the concentration of different drugs dissolved in human serum [32]. This effect is closely linked to the lipophilicity of the drug, and correlates with drugs with logP > 2. In this study, the authors also investigated the relationship between the volume of distribution (VD) of the drug and the decrease in serum drug concentration; however, the contribution of VD to this effect is less than that of lipophilicity[32].

ILEs have been used to treat severe toxicity by different toxins for the past 10 years, and the results have been reported mainly in case reports, observational studies, and experimental studies in animals. For all these reasons, there is even less evidence to support the use of ILEs in non-LA induced toxicity compared with LA toxicity[33].

Below is a summary of the use of ILEs in non-LA-induced toxicity and evidence-based recommendations for their use in different clinical scenarios. The recommendations were rated following the GRADE system (Table 2).

Toxicity due to amitriptyline and other tricyclic antidepressants

Tricyclic antidepressants (TCA) continue to be used both in the treatment of depression and in other indications (sleep disorders, neuropathic pain, migraines, enuresis and attention deficit, among others)[34,35].

TCAs are not selective. Their mechanism of action is based on the inhibition of presynaptic neurotransmitter reuptake in presynaptic terminals, although they also block cardiac fast sodium channels and inhibit, both centrally and peripherally, acetylcholine receptors, among others. Hence the close association between TCA-induced neurological and cardiotoxicity, which causes hypotension, sinus tachycardia due to the vagolytic effect, conduction disturbances, ventricular tachycardia (VT) and ultimately, cardiac arrest[3 4].

The standard treatment for this type of intoxication, in addition to support management, is administration of sodium bicarbonate (standard treatment for sodium channel blocker toxicity). However, some cases are refractory to standard treatment[36]. For this reason, and due to the lipophilicity of these drugs (especially amitriptyline with a LogP of 5.04)[37], lipid emulsions have been suggested as an alternative when standard treatment fails.

The following are the current recommendations for the use of ILEs in the treatment of ATC intoxication developed by the Lipid Emulsion Therapy Workgroup - a collaborative project bringing together several toxicology associations[23]:

- In cardiac arrest due to either amitriptyline or any other TCA toxicity, neutral recommendation (D)
- In very severe toxicity due to TCA, ILEs are not recommended as first line therapy (2D). If toxicity is due to amitriptyline, ILEs are recommended as the last resort, when other treatments have failed (2D)
- In all other cases of TCA toxicity, ILEs are not recommended under any circumstances (2D). In very severe toxicity due to amitriptyline, ILEs are not recommended as first line therapy(1D)

The panel of experts developed these recommendations on the basis of the numerous case reports in which ILEs were used successfully to treat this type of toxicity[38]. However, there is only 1 randomized clinical trial in humans, which was presented in Marseille in 2013 as an abstract, in which ILE did not show benefit in the treatment of antidepressant toxicity, while a study in an animal model published in 2014 showed that hypotension did not improve compared to standard treatment (bicarbonate)[39]. Finally, a study in rats administered an overdose of oral amitriptyline showed that survival decreased compared to standard treatment[40].

For all these reasons, and in the absence of solid evidence, the panel of experts decided, by way of summary, to only recommend ILEs in severe situations that are refractory to standard treatment.

Table 3 Partition coefficient of commonly used beta-blocker drugs.

Drug	Partition coefficient
Carvedilol	4.19
Propranolol	3.48
Metoprolol	2.15
Bisoprolol	1.87
Atenolol	0.16

Beta-blocker toxicity

Beta-blockers are the most widely used cardiovascular drugs in clinical practice due to their beneficial effects in the treatment of arterial hypertension, coronary heart disease, tachyarrhythmias, congestive heart failure, migraine, benign essential tremor, panic attacks, and hyperthyroidism, among other conditions. Despite their moderately good safety profile, cases of toxicity due to overdose are frequent[41].

Beta-blocker toxicity usually presents with cardiovascular symptoms, frequently bradycardia and hypotension, and in severe cases can even lead to complete atrioventricular block, shock, and cardiac arrest. As these drugs act on different systems and organs, they can also cause other symptoms, such as delirium, seizures, coma, respiratory complications such as bronchospasm, and metabolic complications such as hypoglycaemia, the latter being more common in paediatric patients.

The standard treatment for this type of toxicity varies according to the severity, but basically consists of life support plus other pharmacological measures, such as glucagon, high-dose insulin, catecholamines and fluid replacement[42]. Extracorporeal membrane oxygenation (ECMO) is indicated in patients with refractory cardiac arrest[43].

Recent case reports and experimental animal studies have described the use of lipid emulsions to treat beta-blocker toxicity. As with other xenobiotics, ILE effectiveness will depend on the lipophilicity of these drugs, so propanol, metropolol, and carvedilol will be more susceptible to ILE treatment. Other commonly used beta-blockers, such as bisoprolol or atenolol, would not benefit from this treatment (Table 3).

Although some authors have described using ILEs to treat beta-blocker toxicity, the evidence remains scarce and is mainly based on experimental data (in animals) and case reports. Their efficacy has not yet been demonstration in a randomized blinded study. The outcome measured in most

Table 2 Recommendations and degree of evidence.

Grade of recommendation	
Level 1	Strong recommendation. The course of action is considered appropriate by the large majority of experts with no major dissension
Level 2	Weak recommendation. The course of action is considered appropriate by the majority of experts, with some degree of dissension
Neutral	The course of action is neither preferred nor rejected by the majority of experts
No recommendation	The group of experts reached no agreement
Grade system: the 4 degrees of evidence	
A	High level of evidence in the literature
B	Moderate level of evidence
C	Low level of evidence
D	Very low level of evidence

GRADE terminology used by the AACT Lipid Emulsion Therapy Workgroup.

reports describing their use in severe toxicity is survival, suggesting the possibility of publication bias[38].

The current recommendations of the Lipid Emulsion Therapy Workgroup are as follows[23]:

- In cardiac arrest due to lipid-soluble and non-lipid-soluble beta-blockers, the recommendation on the use of ILE is neutral
- In severe toxicity due to lipid-soluble beta-blockers, the recommendation is neutral; if severe toxicity is due to non-lipid-soluble beta-blockers, ILEs should not be used as first line therapy (2D)
- In all other situations, the use of ILEs is not recommended in toxicity due to both lipid-soluble and non-lipid-soluble beta-blockers (2D)

In other words, the panel of experts does not recommend the use of lipid emulsions in general, and leaves their use to the clinician's discretion in severe cases refractory to standard treatment. The main reasons for advising against ILEs in general are: 1) the effectiveness of treatment with high-dose insulin and euglycemia; 2) different degrees of lipid solubility among beta-blockers, which means that ILEs are have little or no effect in many of these drugs, and 3) reports of ILEs obstructing the membranes of extracorporeal membrane oxygenation systems[44].

Bupropion toxicity

Bupropion is an atypical antidepressant that inhibits norepinephrine and dopamine reuptake, but has little or no effect on serotonin (the site of action of most modern antidepressants). Bupropion is rarely used nowadays - its main indications being the treatment of major depressive disorder (as second line therapy in patients with sexual dysfunction), smoking cessation, and in certain cases of obesity[45,46].

Bupropion can be described as having a suboptimal safety profile, and in fact was withdrawn by the FDA but later re-approved for use at far lower doses than originally authorised. Bupropion toxicity generally affects the central nervous system, causing seizures that can progress to coma. In the heart, bupropion blocks voltage-dependent sodium channels, and symptoms of toxicity range from arrhythmias to cardiac arrest[46]. Some cases of bupropion toxicity lasting from 24 to 48 h have been reported[42,46].

Like many other toxins without a specific antidote, bupropion toxicity is treated with supportive care. As its mechanism of action is similar to TCAs and other sodium channel blockers, bupropion has also been successfully treated with bicarbonate, although the evidence is weak[47].

The lipophilic profile of bupropion (logP 3.65) make it susceptible, as mentioned above, to treatment with ILEs, although fewer cases have been reported compared to other xenobiotics. A 2016 review[38] described 5 cases in which ILE administration was effective, but made no mention of studies and animal models. A subsequent study in an animal model reported that ILE alone did not improve survival; however, the combination of ILE and adrenaline achieved greater survival than adrenaline alone[48].

For all these reasons, the panel of experts [23] made the following recommendations for ILE in bupropion toxicity:

- In cardiac arrest, the recommendation is neutral
- In severe toxicity, the use of ILEs is recommended as second line therapy (2D) but not first-line (2D)
- In all other situations, ILEs are not recommended as first line therapy (2D)

Calcium channel blockers

In the US, toxicity induced by cardiovascular drugs is the third leading cause of death due to prescription drugs. Half (50%) of all cardiovascular drug overdoses are caused by calcium channel blockers, a group that includes drugs that act on the SA node (inhibitors such as verapamil an diltiazem) and those that do not (such as the antihypertensives amlodipine, nifedipine, etc.). Of these, verapamil is most frequently associated with severe toxicity.

In 2016, Kryshtal et al. showed that these xenobiotics, being lipophilic, might be eliminated by the lipid sink and shuttle action of ILEs[49]. This has given rise to various case

reports on the use of ILEs to treat calcium channel toxicity, although the results are inconclusive.

The Lipid Emulsion Therapy Workgroup[38] recommendations on ILEs in calcium channel toxicity are as follows:

Diltiazem and verapamil

- In cardiac arrest, the recommendation is neutral
- In severe toxicity, ILEs are recommended as second-line therapy (2D) but not as first-line (2D)
- In all other situations, ILEs are not recommended as first line therapy (2D)

Dihydropyridine calcium antagonists

- In cardiac arrest, the recommendation is neutral
- In severe toxicity, ILEs are not recommended as first line therapy (2D)
- In all other situations, ILEs should not be used under any circumstances (2D)

More recently, a panel of experts[43] updated the recommendations for treating calcium channel blocker toxicity[43], and indicated that ILEs should be reserved for patients refractory to first-line therapy (intravenous calcium, high-dose insulin, epinephrine, norepinephrine, and atropine) -recommendation (2D); patients in refractory *shock* (1D) and in cardiac arrest, in addition to other life support measures.

Cocaine toxicity

Pure cocaine was first isolated in the 1880s, and was the first LA used in eye surgery. Since then, it has been used in different medical indications, although it has currently fallen out of use. Almost all cases of toxicity occur due to use of cocaine as a recreational drug, or accidental rupture of cocaine packages carried internally by body packers. In the US, most cases of recreational drug overdose treated in emergency departments involve cocaine[50].

Cocaine is an amine reuptake inhibitor that acts as an indirect sympathomimetic by increasing neurotransmitter concentration in presynaptic terminals. This produces the typical symptoms of intoxication that include haemodynamic instability with hypertension and tachycardia. As an LA, cocaine acts as both a cardiac and neuronal sodium channel blocker. This severely disrupts cardiac conduction, and manifests on ECG as prolongation of the QRS interval, and clinically as negative inotropy (it competes with the increase in adrenergic tone produced by sympathetic activation)[50].

Acute toxicity due to cocaine overdose is, like other drug overdoses, treated with supportive measures, mainly involving administration of CNS depressants such as benzodiazepines, and hypotensive drugs while avoiding beta blockers as far as possible. This is a generalised, non-specific approach, since there is currently no specific antidote to neutralise the effect of cocaine.

Due to its similarity to LAs and logP of 2.3 (that is, in the range of lipid solubility theoretically susceptible to ILE treatment), some authors have suggested that cocaine toxicity can potentially be treated with lipid emulsions[32].

Only a few case reports have been published describing the treatment of cocaine overdose with ILEs. Cao et al. in 2015[37], and Levine et al. in 2016[38] only describe 3 cases (2 of them in which resuscitation was successful). However, no clinical trials in humans have been published, and only a few studies in animal models have been reported. In 2014, Carreiro et al.[51] found that pre-treatment with ILE reduced the likelihood of cardiac arrest in a rat model of cocaine toxicity. In 2016, however, the same group[52] using the same model of cocaine toxicity found that ILE administered as treatment instead of pre-treatment did not reduce the likelihood of cocaine-induced cardiac arrest. Fettiplace et al., meanwhile, showed that ILE improved cardiac contractility in an isolated rat heart model of cocaine intoxication[53].

All this shows that there is scant, even contradictory, evidence of the efficacy of ILEs in cocaine intoxication. The Lipid Emulsion Therapy Workgroup has made the following recommendations for ILE in cocaine-induced toxicity[23]:

- In cardiac arrest, the recommendation is neutral
- In severe toxicity, ILEs are not recommended as first-line therapy (2D)
- In all other situations, ILEs are not recommended as first line therapy (2D) or as part of treatment modalities (2D)

Diphenhydramine toxicity

Diphenhydramine is a first-generation H1 antihistamine that act on the CNS to produce sedative effects. For this reason, they are not currently used in allergies but rather as a treatment for occasional insomnia.

Its main mechanism of action involves the inhibition of histamine H1 receptors; however, this blockade is not selective, since diphenhydramine also inhibits other receptors, particularly cholinergic receptors and to a lesser extent serotonergic receptors and cardiac voltage-dependent sodium channels[54].

The symptoms of overdose are similar to muscarinic blockade, and include visual disturbances, dry mouth, sedation, convulsions, coma and finally, in severe cases, arrhythmias and cardiac arrest.

This type of toxicity is treated with general measures (decontamination techniques) and cardiopulmonary support. In the event of ventricular arrhythmias, treatment with sodium bicarbonate would be indicated.

Again, there is no specific antidote. Given its logP of 3.4, diphenhydramine could, *a priori*, be a candidate for ILE therapy. So far, 6 case reports with good outcomes have been published[23,54], together with 2 animal studies comparing ILE versus bicarbonate in a diphenhydramine-induced cardiac toxicity swine model. In these experiments, no differences were found between ILE and sodium bicarbonate therapy[39,55].

The Lipid Emulsion Therapy Workgroup has made the following recommendations for ILE in diphenhydramine -induced toxicity[23]:

- In cardiac arrest, the recommendation is neutral

- In severe toxicity, ILEs are not recommended as first-line therapy (2D)
- In all other situations, ILEs are not recommended as first line therapy (2D) or as part of treatment modalities (2D)

Some standard antihistamines share certain pharmacokinetic characteristics with diphenhydramine; however, as there are no reports of ILEs used to treat antihistamine poisoning, their use is not recommended.

Digoxin toxicity

Digoxin has been one of the most widely used drugs in the treatment of heart failure, although it has now fallen into disuse and has been relegated to third-line therapy. Nevertheless, it continues to be widely used as an SA node-inhibitor in supraventricular tachycardia with concomitant heart failure.

Digoxin, however, must be closely monitored due to its narrow therapeutic window, and cases of toxicity are common.

Digoxin is a highly lipid-soluble glycoside with cardiac activity; therefore, by analogy, severe toxicity should respond to ILE therapy.

In 2016, Yurtle et al. performed the first study in a rat model to evaluate the potential use of ILEs in digoxin toxicity, and found that these emulsions prolonged the time until asystole[56]. In 2018, also in a rat model, Turán et al. showed the non-inferiority of ILEs vs DigiFab®, a digoxin-specific monoclonal antibody, in the treatment of digoxin-induced toxicity[57].

Because the aforementioned studies were published later, the ILE expert panel made no recommendations on ILE in digoxin toxicity. Following their methodology, the degree of recommendation for ILE to treat cardiac arrest secondary to digoxin intoxication would probably be 2D.

Class 1 antidysrhythmic toxicity

According to the Vaughan-Williams classification, class I antiarrhythmics act by blocking cardiac voltage-gated sodium channels. The most widely used in our setting are flecainide, propafenone, procainamide and lidocaine. Lidocaine, though used mainly as an LA, is also used to treat certain types of ventricular arrhythmias.

These agents have p̈ro-arrhythmicp̈roperties if overdosed, since they produce alterations in cardiac conduction, causing atrioventricular block, bradycardia, prolongation of the QRS interval, ventricular arrhythmias, and in certain cases, cardiac arrest with ventricular fibrillation or asystole[58].

Excluding lidocaine (which is discussed in the section on LA-induced toxicity), the antidysrhythmic drugs that are susceptible to ILE therapy are flecainide and propafenone, since both have a logP < 2.

Few authors have evaluated the efficacy of ILEs in the context of antidysrhythmic toxicity. In 2016, Levine et al. reported 5 cases of flecainide toxicity with favourable outcomes and 2 cases of propafenone toxicity, also with favourable outcomes[38]. Over a 5-year period, the US National Poison Data System included 21 cases of flecainide toxicity with fatal outcome (despite administration of Intralipid®)[33]. Finally, there is only 1 experimental study in rats in which ILE was compared with sodium bicarbonate; no differences in return to baseline parameters or survival were observed[29]. In a recent case, with a favourable outcome, standard resuscitation measures, including sodium bicarbonate were combined with ILE administration[59].

The Lipid Emulsion Therapy Workgroup has made the following recommendations for ILE in antidysrhythmic toxicity[23]:

- In cardiac arrest, the recommendation is neutral
- In severe toxicity, without cardiac arrest, the recommendation is neutral
- In non-severe toxicity, ILEs are not recommended as first-line therapy (2D)

Other toxins

Since ILEs and their hypothetical mechanism of action were first described in 1998[1], they have been tested in a multitude of toxicities caused by xenobiotic drugs that meet the required liposolubility profile.

The recommendations for the use of ILEs in other less common drugs are:

- In cardiac arrest due to toxicity with ivermectin, antimalarials, antipsychotics, the recommendation for ILEs is neutral.
- In life-threatening situations caused by agents such as baclofen, ivermectin and selective serotonin reuptake inhibitors, the recommendation for ILEs is neutral.
- In life-threatening situations caused by antimalarial and antipsychotic toxicity, ILEs are not recommended as first-line therapy (2D)

Conclusion

Lipid emulsions, particularly Intralipid®, are currently considered essential in the treatment of LA-induced toxicity. Their use is endorsed by several guidelines, particular those published by anaesthesia associations, and ILEs in combination with standard cardiopulmonary resuscitation measures are recommended to treat LA-induced toxicity. Despite this, many authors continue to believe that there is scant evidence to support their use, particularly in the case of toxicity due to LAs other than bupivacaine, and more studies are needed to definitively confirm their effectiveness.

The use of ILEs in non-LA-induced toxicity is even less clear. The results of clinical trials and experimental studies with different toxins are often contradictory. Current evidence suggests that lipid therapy should be used in cases that meet the following characteristics: 1) toxicity caused by fat-soluble xenobiotics, specifically, with an octanol/water partition ratio greater than 2; 2) no specific antidote or one that is largely ineffective; 3) first-line resuscitation mea-

sures have been applied and failed, and 4) the patient's clinical condition is serious.

Funding

The authors declare that they have not received specific aid from agencies in the public sector, commercial sector or non-profit entities.

Conflict of interests

The authors have no conflict of interest to declare.

Acknowledgements

We would like to thank the entire local anaesthetic cardiac toxicity research team from the Department of Medicine and Experimental Surgery of the Gregorio Marañón Hospital, for their efforts and dedicated search for antidotes.

Also, doctoral student Alejandro Alonso Eugenio (alejaalo@ucm.es) for designing the figures used in this manuscript.

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