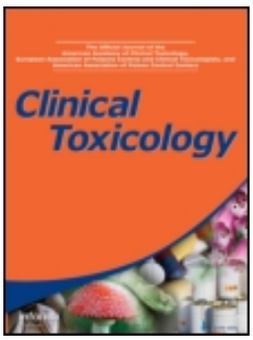

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REVIEW

Systematic review of the effect of intravenous lipid emulsion therapy for non-local anesthetics toxicity

Michael Levine[a], Robert S. Hoffman[b], Valéry Lavergne[c], Christine M. Stork[d], Andis Graudins[e], Ryan Chuang[f], Samuel J. Stellpflug[g], Martin Morris[h], Andrea Miller-Nesbitt[h], Sophie Gosselin[i] and for the Lipid Emulsion Workgroup*

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ABSTRACT

Background: The use of intravenous lipid emulsion (ILE) therapy for the treatment of lipophilic drug toxicity is increasing. Despite this, the evidence for its effect in non-local anesthetic toxicity remains sparse. Furthermore, many case reports describe ILE use for substances in which no clear efficacy data exists. The American Academy of Clinical Toxicology established a lipid emulsion workgroup. The aim of this group is to review the available evidence regarding the effect of ILE in non-LA drug poisoning and develop consensus-based recommendations on the use of this therapy. **Methods**: A systematic review of the literature was performed to capture articles through 15 December 2014. Relevant articles were determined based upon a predefined methodology. Articles involving pre-treatment experiments, pharmacokinetic studies not involving toxicity, and studies not addressing antidotal use of ILE met pre-defined exclusion criteria. Agreement of at least two members of the subgroup was required before an article could be excluded. **Results**: The final analysis included 203 articles: 141 for humans and 62 for animals. These include 40 animal experiments and 22 case reports involving animal toxicity. There were three human randomized control trials (RCT): one RCT examined ILE in TCA overdose, one RCT examined ILE in various overdoses, and one study examined ILE in reversal of sedation after therapeutic administration of inhaled anesthesia. One observational study examined ILE in glyphosate overdose. In addition, 137 human case reports or case series were identified. Intravenous lipid emulsion therapy was used in the management of overdose with 65 unique substances. **Conclusions**: Despite the use of ILE for multiple substances in the treatment of patients with poisoning and overdose, the effect of ILE in various non-local anesthetic poisonings is heterogenous, and the quality of evidence remains low to very low.

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Lipid; non-local anesthetics; systematic review

Introduction

Intravenous lipid emulsion (ILE) therapy involves the administration of a large amount of fat for the purposes of treating drug toxicity due to fat-soluble drugs. The most prevalent of several theories describing the purported mechanism of ILE is the "lipid sink" theory. According to this theory, the administration of lipid reduces the volume of distribution of the drug in question by pulling lipid soluble drugs out of the periphery and into the vascular compartment.[1] Evidence supporting this theory includes an animal study demonstrating rapid distribution of labeled bupivacaine away from the heart after an ILE bolus.[2] However, others have questioned this theory, demonstrating that redistribution alone is insufficient to reverse systemic toxicity.[3] An additional theory is the "change in energy theory", in which ILE provides enough fatty acid to facilitate myocardial free fatty acid utilization. A third proposed theory involves nitric oxide production. Some of the hypotension observed with local anesthetic toxicity may be related to nitric oxide release. The use of ILE may inhibit endothelial nitric oxide synthase, thereby decreasing nitric oxide induced vasodilation.[4] Finally, others have proposed that ILE has a cardiotonic effect.[2,5]

The first human cases of ILE for the treatment of drug toxicity were published in 2006.[6,7] Since then, ILE treatment for both local anesthetic (LA) and non-local anesthetic (non-LA) drug toxicity has significantly increased. Although most of the initial

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cases involved critically ill patients, some authors have suggested a move towards more liberal use of ILE to include patients who are hemodynamically stable.[8,9] Currently available empiric guidelines describe how ILE should be administered,[10] but provide no evidence-based criteria to support indications or dosing of ILE in non-LA toxicity. The American Academy of Clinical Toxicology (AACT) initiated a collaboration between the European Association of Poison Centres and Clinical Toxicologists (EAPCCT), the Asia Pacific Association of Medical Toxicology (APAMT), the Canadian Association of Poison Control Centres (CAPCC), the American College of Medical Toxicology (ACMT) and the American Association of Poison Control Centers (AAPCC) to create the Lipid Emulsion Therapy in Clinical Toxicology Workgroup in order to review all appropriate evidence pertaining to the use of lipid emulsion in toxicology, with the ultimate goal of providing evidence and consensus-based recommendations. The entire workgroup is comprised of 24 members. The ultimate goal was to develop evidence and consensus based recommendations on the use of ILE in poisoning. The primary objective of this review is to report the results of a systematic appraisal of the literature and present the reported effects associated with ILE use in non-LA toxicity. Consensus recommendations will be published in a separate manuscript.

Methods

A working subgroup (the authors) of the lipid emulsion therapy workgroup,[11] was formed to gather and review the evidence on the effect of ILE in the treatment of non-LA drug toxicity. This subgroup was formed based on the best possible match to represent the clinical experts and various stakeholders and involved in the workgroup. It also included two medical librarians who assisted in conducting the systematic searches and the retrieval of potentially eligible publications, as well as an epidemiologist with specific methodological expertise in conducting systematic reviews. Subgroup members divulged all potential conflicts of interests prior to inclusion in the workgroup. All communication was performed by email exchanges and by telephone conferences.

Two medical librarians created a systematic search strategy for Medline (Ovid), which is provided in the Appendix. The strategy comprised a combination of Medical Subject Headings, title/abstract key words, truncations, and Boolean operators, and included the concepts of ILE and toxicology (including but not limited to calcium channel blockers, beta-blockers, and sodium channel blockers). It was subsequently translated for Embase (via Ovid), CINAHL (via EBSCO), BIOSIS Previews (via Ovid), Web of Science, Scopus, and the Cochrane Library/DARE. All databases were searched from inception to 15 December 2014. Subsequently, articles were triaged into local anesthetics and non-local anesthetics for review by each designated groups.

In addition, conference abstracts from the European Association for Poison Centers and Clinical Toxicologists, and the North American Congress of Clinical Toxicology (both from 2000 to 2014) and previous reviews were hand-searched by various group members. Abstracts from the Asia Pacific Association of Medical Toxicology were searched in the same way from 2007 to 2014. Group members also performed cross-referencing of full-text articles. No limits were applied for language, and candidate studies in languages not known to any of the authors were translated.

In summary, the criteria for publication inclusion in the evaluation of the effect of ILE include studies in humans and animals to whom ILE was given for the purpose of treating poisoning, and exclusion criteria are non-original data, animal studies with methods and results that cannot be extrapolated or are uninterpretable to humans, pre-treatment models, and experimental *in vitro* or *ex vivo* models. A complete methodology of the larger project of which this systematic review is one part has been previously published,[11] and describes in detail all relevant methodological aspects such as clinical questions, search strategies, eligibility of publications, data extraction and summary, and assessment of the risk of bias. The GRADE methodology was used to appraise the quality of the evidence.[12–14]

The log *D*, which is based on the partition coefficient, and is a measure of lipophilicity, is reported for each substance. The degree of lipophilicity directly corresponds with the Log *D*; as the Log *D* increases, so does the lipophilicity of a substance. Unless specifically mentioned, all mentions of ILE refer to a 20% preparation.

Results

The final analysis included 203 articles, of which 62 involved animals and 141 involved humans (Figure 1).

There were three human randomized controlled trials (RCTs) each evaluating different substances (Table 1).[15–17] The first RCT examined the efficacy of ILE in the reversal of coma after lipophilic drug overdose.[17] This study, which included both lipophilic and non-lipophilic substances, randomized 30 patients to receive standard supportive therapy with ($n = 15$) or without ILE ($n = 15$).[17] The specific substances included numerous medications such as benzodiazepines, tricyclic antidepressants (TCA), anticonvulsants, anticholinergics, antihistamines, muscle relaxants, selective serotonin reuptake inhibitors, antipsychotics, acetaminophen, non-steroidal anti-inflammatory drugs, salicylates, and opioids. The ILE group had a mean (±standard deviation) improvement in the Glasgow coma scale (GCS) of 3 ± 1, while the controls had a mean (±SD) GCS improvement of 2 ± 2 ($p = 0.048$). The authors reported this difference as both statistically and clinically significant and advocated ILE administration in all overdoses. Nevertheless, this study contains several methodological shortcomings. The authors report means with standard deviation, rather than medians with interquartile ranges. Furthermore, they never show the distribution of the GCS before and after ILE, only the mean differences. In addition, the study was unblinded, there was a potential overestimation of the expected effect of the intervention in sample size calculation, and patients were excluded and replaced after randomization. Finally, there was incomplete reporting (e.g., the absence of information on comparative poisoning, incomplete information on the intervention of interest, and selective reporting of GCS difference without presenting potential confounders). These limitations preclude any clear interpretation of the reported results. The second RCT [15] compared ILE to standard care in patients with reported TCA ingestions. The treatment group received ILE in addition to standard measures

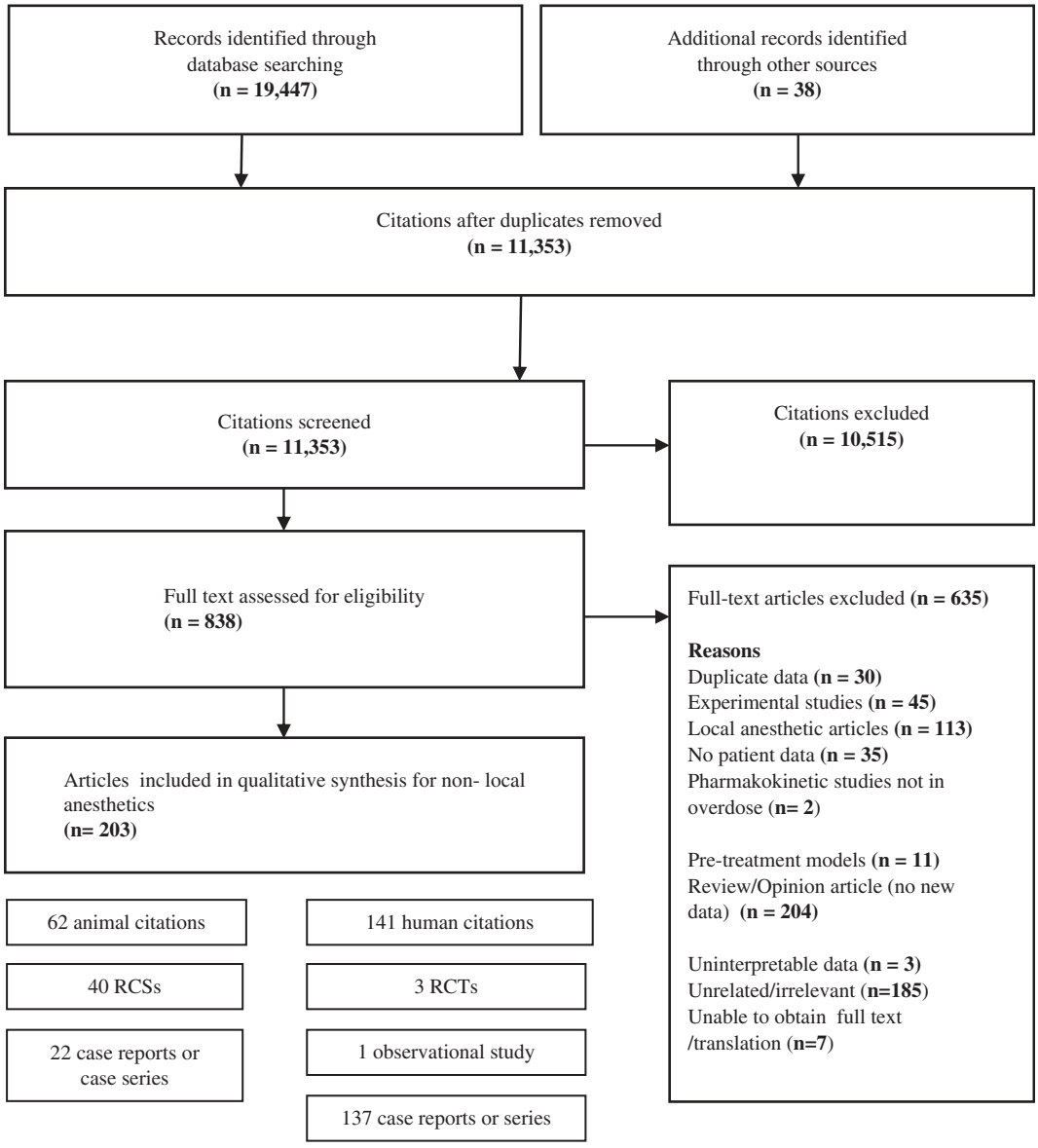

Figure 1. Selection of articles flow diagram. Search date: 15 December 2014. RCS: randomised controlled studies; RCT: randomised controlled trials.

including sodium bicarbonate. A total of 108 patients were randomized with 54 patients in each treatment group. No differences were found in the blood pressure at the time of ECG reversal or days of hospitalization, however, the time to reversal of the ECG was 20 min shorter in the intervention group. No statistical features or doses of antidotes were reported in this study, which was only available in abstract form. The last RCT [16] enrolled 66 patients and while under general anesthesia with isoflurance, administered 2 mL/kg of 20% ILE versus 0.9% saline to measure the time of awakening post-anesthesia. Although the authors report a positive effect on the time and quality of recovery time (difference of approximately 4 min between groups), there was no difference in the time to extubation. The subtoxicity design as well as the small sample size limits the extrapolation of these results to the overdose clinical scenario. Each of these studies is further described below in their respective substance section.

The single observational study [18] evaluated the potential therapeutic effects of 20% ILE for acute glyphosate ingestion. Sixty-four patients were enrolled with allocation to two groups, those who had received ILE ($n = 22$) and those who received supportive care without ILE ($n = 42$). Control patients ($n = 22$) were selected separately from the other group to match the estimated amount of glyphosate ingested and the time from ingestion to presentation. The authors attempt to further distinguish their patients by creating categories per amount of glyphosate ingestion (<100 mL or more than 100 mL). The amount of lipid emulsion for the low-dose ingestion was 20 mL/h and for the high dose ingestion 500 mL followed by 1000 mL over the next 24 h. No differences were observed on the incidence of mental status changes, kidney failure, respiratory failure but lower incidence of dysrhythmias and hypotension was reported in the ILE-treated groups. This study has serious limitation by study design with the risk of selection bias and the imprecision of the estimation of ingested dose and the arbitrary cut-off of 100 mL for the group division. This study is further discussed below in the section on pesticides.

Table 1. Summary of estimates with associated GRADE ratings for human controlled studies reporting the effect of ILE on non-LA toxicity.

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[c]	GRADE rating
Mortality							
$N = 1$ [18]	Acute glyphosate toxicity	ILE ($n = 22$)	Historical controls not receiving ILE ($n = 22$)	RD of mortality $= -0.05$ (NA) ($p =$ NS)	No difference in mortality between groups	Observational study; Limitations due to potential selection bias (historical controls) (−1) and due to potential information bias (imprecision in estimating matching variables and reporting of clinical outcomes) (−1), Imprecision due to small sample size (−1)	Very low
$N = 1$ [15][a]	Severe TCA toxicity	Standard treatment + ILE ($n = 54$)	Standard reatment + bicarbonate ($n = 54$)	RD of mortality $= -0.02$ (NA) ($p =$ NS)	No difference in mortality between groups	RCT; Downgrade: Limitation due to incomplete reporting of methods (−2), Imprecision due to incomplete reporting of results (−1)	Very low
Cardiotoxicity							
$N = 1$ [17]	Various non-local anesthetic drug intoxication with a Glasgow Coma Scale ≤ 9	10 mL/kg intralipid 10% infusion ($n = 15$)	No ILE ($n = 15$)	MD in systolic blood pressure (mmHg) $= -5.0$ (−18.1; +8.1); MD in pulse rate (bpm) $= -7.0$ (−18.6; +4.6); MD in mean rate pressure product (RPP) $= -1091$ (−2853; +671)	No difference in systolic blood pressure, pulse rate and mean rate pressure product between groups	RCT; Limitation due to potential selection bias (exclusion and replacement after randomization, incomplete reporting of patients' poisoning), due to lack of blinding and due to selective reporting of outcomes (−2), Imprecision due to small sample size (−1)	Very low
$N = 1$ [18]	Acute glyphosate toxicity	ILE ($n = 22$)	Historical controls not receiving ILE ($n = 22$)	RD of hypotension $= -0.41$ (NA) ($p = 0.002$); RD of dysrhythmias $= -0.23$ (NA) ($p = 0.05$)	Group receiving ILE experienced less hypotension and dysrhythmias than controls	Observational study; Limitations due to potential selection bias (historical controls) (−1) and due to potential information bias (imprecision in estimating matching variables and reporting of clinical outcomes) (−1), Imprecision due to small sample size (−1)	Very low
$N = 1$ [15]	Severe TCA toxicity	Standard treatment + ILE ($n = 54$)	Standard treatment + bicarbonate ($n = 54$)	Data not shown except for MD in time needed for EKG reversal (minutes) $= -20$ (NR) (reported $p =$ NS)	No difference in time needed for ECG reversal and in blood pressure at the time of ECG reversal between groups	RCT; Downgrade: Limitation due to incomplete reporting of methods (−2), Imprecision due to incomplete reporting of results (−1)	Very low
Neurotoxicity							
$N = 1$ [17]	Various non-local anesthetic drug intoxication with a Glasgow Coma Scale ≤ 9	10 mL/kg intralipid 10% infusion ($n = 15$)	No ILE ($n = 15$)	MD in improvement of Glasgow Coma Scale (6 h after admission versus baseline) $= +1.0$ (−0.2; 2.2) (reported $p = 0.048$)[d]	Group receiving ILE infusion experienced a greater neurological improvement as compared to controls	RCT; Limitation due to potential selection bias (exclusion and replacement after randomization, incomplete reporting of patients' poisoning), due to lack of blinding and due to selective reporting of outcomes (−2), Imprecision due to small sample size (−1)	Very low

(continued)

Table 1. Continued

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[c]	GRADE rating
$N=1$ [18]	Acute glyphosate toxicity	ILE ($n=22$)	Historical controls not receiving ILE ($n=22$)	RD of mental change $=+0.05$ (-0.22; $+0.31$); RD of seizure $=-0.05$ (NA) ($p=$ NS)	No difference in mental change or seizures between groups	Observational study; Limitations due to potential selection bias (historical controls) (-1) and due to potential information bias (imprecision in estimating matching variables and reporting of clinical outcomes) (-1), Imprecision due to small sample size (-1)	Very low
$N=1$ [16]	Inhaled isoflurane anesthesia for a laparoscopic cholecystectomy	2 mL/kg of 30% ILE at the completion of skin closure and discontinuation of isoflurane ($n=30$)	Saline ($n=30$)	MdD in time to eye opening (minutes) $=-4.5$ (NR) (reported $p=0.01$); MdD in time to extubation (minutes) $=-4.0$ (NR) (reported $p=$ NS); MdD in time to exit the OR (minutes) $=-4.1$ (NR) (reported $p=0.04$); MdD in time to onset of a MAPARS ≥ 9 (minutes) $=-5.1$ (NR) (reported $p=$ NS). Comparative curves of VAS, OAA/S and MMSE scores with time was significantly better in the ILE group (reported $Ps=<0.01, <0.01$, and 0.04, respectively)	Group receiving ILE experienced a more rapid recovery and better-perceived as compared to controls	RCT; Indirectness due to subclinical toxicity design (-1), Imprecision due to small sample size for secondary outcomes(-1)	Low
Respiratory toxicity							
$N=1$ [18]	Acute glyphosate toxicity	ILE ($n=22$)	Historical controls not receiving ILE ($n=22$)	RD of acute respiratory failure $=-0.18$ (-0.42; $+0.06$); RD of mechanical ventilator $=-0.14$ (-0.32; $+0.05$)	No difference in acute respiratory failure or need for mechanical ventilation between groups	Observational study; Limitations due to potential selection bias (historical controls) (-1) and due to potential information bias (imprecision in estimating matching variables and reporting of clinical outcomes) (-1), Imprecision due to small sample size (-1)	Very low
$N=1$ [17]	Various non-local anesthetic drug intoxication with a Glasgow Coma Scale ≤ 9	10 mL/kg intralipid 10% infusion ($n=15$)	No ILE ($n=15$)	MD in respiratory rate (breaths/min) $=+2.0$ (0.1; 3.9) (reported $p=$ NS)[c]; MD in elapsed time between intubation and extubation (hours) $=-9.0$ (-24.0; 6.0)	No difference in respiratory rate and elapsed time between intubation and extubation between groups	RCT; Limitation due to potential selection bias (exclusion and replacement after randomization, incomplete reporting of patients' poisoning), due to lack of blinding and due to selective reporting of outcomes (-2), Imprecision due to small sample size (-1)	Very low

(continued)

Table 1. Continued

No. of studies	Population	Comparison: Intervention (No. of patients)	Comparison: Comparator (No. of patients)	Summary of finding: Summary estimate[a]	Summary of finding: Interpretation	Quality of evidence: Quality assessment[c]	Quality of evidence: GRADE rating
Renal toxicity							
$N = 1$ [18]	Acute glyphosate toxicity	ILE ($n = 22$)	Historical controls not receiving ILE ($n = 22$)	RD of acute kidney failure = −0.14 (NA) (NS)	No difference in acute kidney failure between groups	Observational study; Limitations due to potential selection bias (historical controls) (−1) and due to potential information bias (imprecision in estimating matching variables and reporting of clinical outcomes) (−1), Imprecision due to small sample size (−1)	Very low

[a]Abstract only.
[b]Quality assessment according to the GRADE methodology. No studies could be pooled together since they were all performed in very different contexts. Also, since no studies were pooled to answer a specific clinical question, inconsistency and publication bias were not evaluable.
[c]Summary estimate is expressed in difference between the "group intervention – group comparator". Either a risk difference (RD), a mean difference (MD) or median difference (MdD) was reported.
[d]Discrepancies are due to the fact that the article reported means with standard deviations, while calculating p values with non-parametric tests.
MAPARS: Modified Aldrete Post-Anesthesia Recovery score.

The remainder of the human literature is quite heterogeneous and we present here a few examples. Cave and colleagues reported a prospective registry of 38 consecutive cases of poisoning with non-LA substances, 30 patients (79%) received ILE for central nervous system (CNS) depression without hemodynamic instability.[19] None of those receiving ILE purely for CNS depression died. Of the eight cases receiving ILE for cardiovascular (CVS) collapse, three (37.5%) died. Among the 30 patients who received ILE for CNS depression, the treating clinician felt ILE contributed to improvement in 26/30 (86.6%) of cases.[19] Due to variability in the amount of ILE administered and the non-randomized nature of this study, no definitive conclusions can be reached and due to the absence of a controlled group is considered a case series.

In a multi-center, retrospective chart review of inpatients with drug-induced cardiotoxicity at three tertiary care referral medical centers,[20] the authors identified nine cases of ILE administration. There were four deaths in this group. The substances most often implicated in poisoning were verapamil, amlodipine, and TCAs. Inadequate information was provided on each patient, and the effect of ILE in the treatment of each case is unclear.

In a case series, ILE was administered to 10 emergency department patients with suspected overdoses.[21] Substances included amitriptyline, metoprolol, quetiapine, bonsai, a combination of nifedipine, fluoxetine, and alprazolam, and a combination of lamotrigine and sertraline. Seven patients had an improvement in blood pressure and heart rate following ILE administration although the exact measured changes were not reported.

Several poison center-based case series are published. In one case series involving five patients, four received ILE for non-LA toxicity.[22] There was insufficient information provided about ILE administration, or the cases in general, to permit meaningful interpretation of outcomes. Downes and colleagues describe their single-center experience with ILE administration for baclofen ($n = 2$), carbamazepine ($n = 1$), and quetiapine ($n = 6$) poisoning.[9] ILE use did not result in a clinical improvement in any of the cases. Jovic-Stosic and colleagues describe ILE administration in nine patients with cardiovascular collapse. In their prospectively collected case series, the toxins identified include one case of glyphosate/polyethyloxylated tallow amine herbicide poisoning, three cases of verapamil with benzodiazepines, two propranolol poisonings mixed with alcohol or psychoactive substances ($n = 2$), and three poly-drug ingestions.[23] Improved blood pressure occurred in all cases although it was transient in some. In one case of verapamil toxicity, acute respiratory distress syndrome (ARDS) developed, which the authors felt might be attributable to ILE use. Improved mental status occurred in seven of the nine cases, although there was no change in rhythm disturbances.

The animal literature contains 40 randomized controlled studies (RCSs) [24–63] and 22 case reports or case series [64–85] reporting the use of ILE for drug toxicity. Among the 40 controlled experiments, TCAs comprised the most common studied class of drugs. Among the 22 animal case reports/case series, the majority of reports involved ivermectin or

Table 2. Summary of animal data for which ILE was used in acute toxicity.

Class of substance and references	Substance	Studies (*n*)	Case reports (*n*)	Total animals (*n*)
Antidysrhythmic [30]	Flecainide	1	0	20
Beta-blocker				
[41]	Metoprolol	1	0	20
[28,44]	Propranolol	2	0	34
[29]	Atenolol	1	0	20
[49]	Propanolol/Clonidine	1	0	36–48
Calcium channel blocker				
[81]	Diltiazem	0	1	1
[35,83]	Nifedipine	2	0	25
[24,54,56,57]	Verapamil	4	0	133
Insecticide/antiparasitic				
[65]	Avermectin	0	1	1
[53]	Chlorpyriphos	1	0	49
[51]	Diazinon	1	0	24
[37]	Dichlorvos	1	0	48
[68,71,73,75,79,84,85]	Ivermectin	0	7	17
[64]	Ivermectin + Praziquantel	0	1	1
[64,72,77]	Moxidectin + Praziquantel	0	3	4
[36]	Parathion	1	0	18
[67,74,76,80,82]	Permethrin	0	5	11
[25,33,58]	Malathion	3		120
GABA agonists			3	
[64,70,78]	Baclofen	0	0	8
[46]	Pentobarbital	1	0	NR
[38]	Propofol	1	0	NR
[32,43,47]	Thiopental	3		55
Miscellaneous substances				
[27]	Dabigatran	1	0	20
[26]	Digoxin	1	0	15
[60]	Diphenhydramine	1	0	36
[63]	Etomidate	1	1	40
[66]	Ibuprofen	0	1	1
[50]	Haloperidol	1	0	30
[34]	Phenytoin	1	0	20
[59]	Tramadol	1	0	30
Tricyclic antidepressants				
[45,48,55,61]	Amitriptyline	4	0	94
[31,39,40,42,62]	Clomipramine	5	0	109
[52]	Desipramine	1	0	56

NR: Not reported.

permethrin. Table 2 summarizes the experimental studies and case reports involving animals treated with ILE.

Antidysrhythmics

Table 3 summarizes the human case reports involving the use of ILE in the treatment of antidysrhythmic toxicity not belonging to Vaughan Williams class II or IV.[86–95] The majority of human experience is with flecainide and propafenone.

Only a single animal study was found for this class of medication.[30] In a rabbit model of flecainide toxicity, Cave and colleagues compared ILE with hypertonic sodium bicarbonate. Toxicity was induced in 20 rabbits via an infusion of intravenous flecainide until the MAP was 60% of its baseline. The authors found no difference between the groups with regards to heart rate, mean arterial pressure, or QRS duration. The rate of seizures was not reported.

Anticoagulants

There are no human trials or case reports examining the effect of ILE in treatment of anticoagulant toxicity in humans.

In a rodent model of orally administered dabigatran (15 mg/kg), the mean bleeding time increased from 110 s at baseline to 271 s after the administration of dabigatran ($p < 0.0001$). However, the administration of ILE did not result in a difference in bleeding time compared with controls.[27]

Anticonvulsants

There are no controlled human studies evaluating the effect of ILE in anticonvulsant drug toxicity. Table 4 summarizes the nine human case reports involving the use of ILE in the treatment of anticonvulsant toxicity, including three cases involving carbamazepine and six cases involving lamotrigine.[22,96–103]

Chu and colleagues performed a rodent survival model of intravenous phenytoin toxicity. Toxicity was considered present when the mean arterial pressure was 50% of its baseline. After toxicity was established, the rats received either ILE or 0.9% saline.[34] Survival occurred in 1/10 ILE treated rats and 2/10 saline-treated rats. There was no difference between treatment groups in either hemodynamics or the number of animals that survived to 1 h.

Antihelminthics/insecticides/herbicides/pesticides

Gil and colleagues compared 22 patients with acute glyphosate toxicity receiving ILE as part of their treatment with 22 historical controls. Subjects were matched with historical controls not receiving ILE based on the amount of glyphosate ingested and

Table 3. Summary of human case reports involving antidysrhythmics outside Vaughan Williams class II or IV, treated with ILE ($n = 9$).

Reference	Drug	Log D[b]	Symptoms	Other Treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[92][a]	Acebutalol Flecainide	0.52 0.55	WCT "Cardio-Circulatory collapse"	Bicarbonate Defibrillation ECMO Epinephrine Glucagon	NR	NR	NR	Survived
[89][a]	Ajmaline	−0.83	Cardiac arrest	Bicarbonate Defibrillation ECMO "Standard guidelines"	1 mL/kg	0.25 mL/kg/min for unknown duration	NR	Survived
[87]	Flecainide	0.55	↓ HR IVCD ↓ BP	Atropine Bicarbonate Fluid resuscitation Magnesium	100 mL	1 L	Improved	Survived
[93]	Flecainide	0.55	CNS ↓ ↓ BP Seizure Cardiac arrest	Bicarbonate ECMO Fluid resuscitation "Vasopressors"	NR	NR	Improved over hours	Survived
[90]	Flecainide	0.55	CNS ↓ ↓ BP ↓ HR	Bicarbonate	1.5 mL/kg	0.25 mL/kg for unknown duration	Improved	Survived
[91][a]	Flecainide	0.55	↓ BP CNS ↓	Atropine Bicarbonate Atropine Dopamine Epinephrine Glucagon	1.5 mL/kg	0.25 mL/kg over 1 h	Improved	Survived
[95]	Propafenone	2.39	Vomiting Seizure IVCD Asystole	Benzodiazepines Bicarbonate Calcium Glucagon Epinephrine Norepinephrine	100 mL	100 mL/h for a total of 1 L	Improved within 1 h	Died of CNS injury
[88]	Propafenone	2.39	↓ BP CNS ↓ IVCD	Bicarbonate Dopamine Epinephrine Fluid resuscitation Epinephrine	100 mL	1050 mL/h × 30 min	Improved	Survived
[86][a]	Propafenone	2.39	CNS ↓ ↓ HR Cardiac arrest	Atropine Calcium Glucagon	90 mL	NR	Improved	Survived

ADR: Adverse drug effects, ↓ BP: hypotension, ↓ HR: bradycardia, CNS ↓: central nervous system depression; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

the interval between exposure and hospital arrival. Hypotension was defined as a systolic blood pressure ≤ 90 mmHg. None of the 22 patients receiving ILE experienced hypotension, while 41% of the control group was hypotensive ($p = 0.002$). Dysrhythmias were also more frequent in the control group (0% and 23%, $p = 0.05$). However, other clinical parameters were comparable between ILE and control groups: change in mental status (32% versus 27%), acute kidney injury (0% versus 14%), respiratory failure (14% versus 32%), and death (0% versus 5%).[18] Despite attempting to control for potential confounders, such as matching for the estimated amount of glyphosate ingested and self-reported drug ingestion histories, inaccuracies may have influenced the results (Table 1).[104]

There are currently no controlled human studies examining the effect of ILE in toxicity due to antihelminthic poisoning. Table 5 summarizes the human case reports involving the use of ILE in the treatment of antihelminthic, insecticide, and pesticide toxicity.[105–109]

Five animal experiments report the effect of ILE in the treatment of either dichlorvos,[37] parathion,[36] and malathion toxicity.[25,33,58] Numerous animal case reports and case series describe ILE for the treatment of antihelminthic toxicity in particular, with ivermectin [64,68,69,71,73,75,84,85] and moxidectin [64,72,77] poisoning.

Gang and colleagues evaluated the toxicity of intraperitoneal dichlorvos in a rodent model. In their study, rats received 0.9% saline; 5 mL/kg ILE; atropine and pralidoxime; or ILE plus atropine and pralidoxime.[37] Outcomes included clinical manifestations, cholinesterase activity and survival. Whereas ILE alone offered no benefit for outcome parameters, the combined use of lipid and standard care significantly increased survival (1/12, saline, 2/12, ILE: 6/12, atropine plus pralidoxime; 11/12, ILE plus atropine plus pralidoxime) and clinical parameters without altering cholinesterase activity.

Another animal study examined the effect of ILE in parathion toxicity. Animals receiving parathion alone (control arm) demonstrated a steady decline in respiratory rate and tidal volume and progression to apnea. Animals treated with 20% ILE five minutes after parathion exposure had a similar mean time to apnea as controls. However, animals treated with ILE 20 min post-exposure had a delay to the onset of apnea compared to controls (95 versus 51 min).[36]

Celikel and colleagues evaluated malathion toxicity in a rodent study.[33] In their study, rats received 1150 mg/kg

Table 4. Summary of human case reports involving antiepileptic toxicity treated with ILE ($n = 9$).

Reference	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[22][a]	Carbamazepine	2.67	↓ BP Seizures	Unknown	NR	NR	NR	Survived
[99][a]	Carbamazepine	2.67	CNS ↓ ↓ BP Seizure Cardiac arrest	Bicarbonate Fluid resuscitation Phenobarbital	1.5 mL/kg	NR	Improved	Survived
[103][a]	Carbamazepine	2.67	CNS ↓ ↓ BP Seizure Cardiac arrest	Bicarbonate Epinephrine Fluid resuscitation Metaraminol Multi-dose charcoal	150 mL	350 mL over 30 min	Unclear	Survived
[96]	Lamotrigine	−0.19	CNS ↓ IVCD	Bicarbonate Magnesium	1 mL/kg	1.5 mL/kg over 20 min	Improved	Survived
[97]	Lamotrigine	−0.19	Seizure CNS ↓ WCT	Benzodiazepines Phenobarbital	100 mL	400 mL over 4.4 h	Transiently improved	Survived
[98]	Lamotrigine Venlafaxine Diazepam	−0.19 0.70 3.86	CNS ↓ Seizure Rigidity Hyper-reflexia	Benzodiazepines Thiopental	2.5 mL/kg	NR	Improved	Survived
[100][a]	Lamotrigine	−0.19	CNS ↓ Seizure	NR	NR	NR	NR; increased clearance	Survived
[101][a]	Lamotrigine	−0.19	Seizure CNS ↓ WCT Cardiac arrest	Amiodarone Benzodiazepines Bicarbonate Calcium Cardioversion Lidocaine Phenobarbital	300 mL	NR	NR	Died
[102]	Lamotrigine Bupropion	−0.19 3.08	Seizure CNS ↓ WCT Cardiac arrest	Amiodarone Bicarbonate Calcium Epinephrine Norepinephrine Vasopressin	100 mL × 2	NR	Improved	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

Table 5. Summary of human case reports involving antihelminths, insecticides, and pesticides treated with ILE ($n = 5$).

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[108]	Endosulfan	3.87	CNS ↓ Seizure ↓ BP Cardiac arrest	Benzodiazepine Bicarbonate Fluid resuscitation Phenytoin Norepinephrine	1.5 mL/kg	1.5 mL/kg over 20 min	Transiently improved	Died
[106]	Glyphosate	−6.66	↓ BP ↑ HR	Calcium Insulin Norepinephrine Vasopressin	100 mL daily x3 days	None given	Not improved	Survived
[105]	Glyphosate	−6.66	CNS ↓ ↓ HR ↓ BP	Atropine Dobutamine Dopamine	100 mL	400 mL over 4.4 h	Improved	Survived
[109]	Glyphosate	−6.66	CNS ↓ ↓ BP Cardiac arrest	Norepinephrine	1.5 mL/kg	0.25 mL/kg over 20 min	Unclear	Survived
[107][a]	Parathion	NA	↓ BP CNS ↓ Seizure Cardiac arrest	Atropine Amiodarone Fluid resuscitation "Inotrope" Phenytoin Pralidoxime	1.5 mL/kg × 2	100 mL over unspecified time	Improved	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NA: not available; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

malathion via orogastric tube in order to induce toxicity. Following the administration of malathion, the rats were assigned to one of five treatment groups: (1) control (no malathion); (2) malathion and physiological serum; (3) malathion and ILE; (4) malathion, atropine, and pralidoxime; (5) malathion, ILE, atropine, and pralidoxime. Administration of 12.4 mL/kg of 20% ILE as a single agent did not alter the onset of toxicity compared to malathion alone. At the end of an 8-h observation period, the combination of ILE with atropine and pralidoxime resulted in some reduction in toxicity.[33] In two further rodent studies, ILE was beneficial in reducing oxidant stress during malathion toxicity. However, the effect was most beneficial when ILE was administered concurrently with malathion, and declined with delay to its administration.[25,58] In a rodent model of oral diazinon toxicity (480 mg/kg), animals received 10% ILE, 20% ILE, or one of two doses of normal saline. There was no difference in reduction in muscle strength, the presence of diarrhea, and mortality between the groups.[51]

Ozkan and colleagues evaluated the effect of oral ILE on neurotoxicity, acetylcholinesterase activity, and oxidative stress in a rodent model of acute oral chlorpyriphos toxicity.[53] Immediately following the administration of chlorpyriphos, the animals received caffeic acid phenethyl ester (CAPE), an acetylcholinesterase inhibitor and ILE. Chlorpyriphos and CAPE each inhibited acetylcholinesterase activity which was additive when given together, while ILE alone did not have any effect on acetylcholinesterase activity. ILE reduced the degree of acetylcholinesterase inhibition that occurred with chlorpyriphos poisoning and decreased the severity of histological cerebellar neurodegeneration.

There are numerous veterinary case reports of ILE use in the treatment of permethrin toxicity.[67,74,76,80,82] In a case report of severe avermectin toxicity in an Australian Shepherd dog, there was no improvement noted following administration of ILE. The animal was then treated with continuous renal replacement therapy using a dialysate containing 5% lipid solution for 6 h. Serum avermectin concentration fell by 29% after dialysis. However, the authors did not report any parameters assessing the effectiveness of extracorporeal removal of avermectin. The dog survived but remained intubated for 3 days.[65]

Beta-blockers

There are no controlled human studies evaluating ILE for the treatment of beta-blocker (BB) toxicity. Table 6 summarizes the human case reports involving the use of ILE in the treatment of BB toxicity.[92,110–128]

In a rabbit model of propranolol, toxicity in which 40 mg/kg of propranolol was administered directly into the small intestine, Harvey and colleagues compared ILE with high-dose insulin euglycemia therapy (HIET).[41] In their study, HIET resulted in significant improvement in the rate pressure product at 60 min compared with the ILE. There was no difference in mortality between groups. In another rabbit model, in which toxicity was induced with a continuous intravenous propranolol infusion, animals subsequently received either 6 mL/kg of 20% ILE or 0.9% saline. Mean arterial pressure was significantly higher in the ILE-treated animals at 15 min (median 69 mmHg versus 53 mmHg, $p = 0.029$), although no differences in heart rate were observed. The study did not continue beyond 15 min.[44] In a study examining the effect of ILE on clonidine or propranolol infusion, rats received clonidine or normal saline. Each rat then received 1 mL/kg of normal saline or 15–20 mg/kg of propranolol. Treatment arms were one of: 1 mL/kg of 20% ILE, 2 mcg/kg of epinephrine, or 1 mL/kg of 0.9% saline. None of the rats treated with 0.9% saline after propranolol and clonidine survived. Only 2/6 of those treated with epinephrine after propranolol and clonidine survived. However, 7/8 rats receiving propranolol alone or propranolol with clonidine followed by ILE survived to 30 min.[49]

In a rabbit model of atenolol toxicity (defined as achieving 60% of baseline mean arterial pressure 60%), each animal received 6 mL/kg of 20% ILE or an equal volume of 0.9% saline once toxicity developed. Only six of 10 rabbits in the ILE group survived to this predefined toxicity endpoint whereas eight of 10 in the saline group survived. There were no differences in MAP or pulse rate between the groups. However, the authors report a *post-hoc* analysis describing a small, but significant difference in MAP from toxicity to immediately post-resuscitation (+7 mmHg for ILE and −3 mmHg for control), which was not sustained at 15 min.[29]

Browne and colleagues assessed metoprolol toxicity in a rabbit experiment. The rabbits received ILE or 0.9% saline after metoprolol toxicity was induced by intravenous infusion.[28] There was no difference between the groups with regards to MAP or heart rate.

Calcium channel blockers

There are no controlled studies in humans evaluating ILE for the treatment of calcium channel antagonists CCB toxicity. Table 7 summarizes the human case reports involving the use of ILE in the treatment of CCB toxicity.[111,112,114,125,127,129–165]

Most animal studies primarily examine poisoning with verapamil.[24,54,56,57] One rodent study examined the effect of ILE in nifedipine toxicity. Five minutes after induction of toxicity, rats were randomized to receive either 18.6 mL/kg of 20% ILE ($n = 10$) or 0.9% saline ($n = 10$). There was no difference in survival, heart rate, MAP, or base excess.[35] A swine study examined the effects of ILE in nifedipine toxicity. When cardiac arrest was felt to be imminent, animals received 17 mL/kg of 20% ILE. Comparing the systemic vascular resistance (SVR) 10 min after lipid vs. before lipid, there was a significant decrease in the SVR post-lipid (164 ± 205 versus 558 ± 261 dyne-s/cm^5). There was no statistically significant difference with regards to heart rate, mean arterial pressure, central venous pressure, and cardiac output.[83]

Using a rodent model of continuous verapamil infusion, Perez and colleagues attempted to ascertain to optimal dose of ILE required to improve toxicity. The MAP was highest using 24.8 mL/kg, which achieved an increase of 43 mmHg versus placebo (95% CI 16–70 mmHg) higher with ILE starting at 30 min (95% CI 5.6–44.7 mmHg) and sustained at 60 min versus the 6.2 mL/kg dose (95% CI 18–86 mmHg). This same dose of 24.8 mL/kg was also associated with the greatest improvement in heart rate, and base excess, while a dose of 18.63 mL/kg resulted in the longest mean survival time.[54] All ILE doses were in excess of those recommended in human toxicity.

Table 6. Summary of human case reports of beta antagonist toxicity treated with ILE ($n = 21$).

Reference	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[92][a]	Acebutolol	2.59	Ventricular tachycardia Asystole	Epinephrine Glucagon Sodium bicarbonate	NR	565 mL over 2 h	Unclear	Survived
[114][a]	Atenolol	−2.03	↓ BP	Calcium Dopamine Fluid resuscitation IABP Insulin Norepinephrine Pacemaker	1.5 mL/kg	0.25 mL/kg/min for 30 min, later for 60 additional minutes	Transiently improved	Died
[117]	Atenolol	−2.03	↓ BP ↓ HR	Atropine Fluid resuscitation Glucagon	NR	1 L over 2 h	Improved	Survived
[122][a]	Atenolol Amlodipine Valsartan Carbon monoxide	−2.03 2.00 −0.34 NA	↓ BP	Calcium Dopamine Epinephrine Glucagon Fluid resuscitation Insulin Methylene blue Phenylephrine	1.5 mL/kg	NR	No response	Survived
[121][a]	Atenolol Amlodipine Zolpidem	−2.03 2.00 2.35	↓ BP Cardiac Arrest	Calcium Dopamine Fluid resuscitation Insulin Methylene blue Norepinephrine Phenylephrine Vasopressin	1.5 mL/kg	NR	No response	Died
[110][a]	Carvedilol	3.16	↓ BP	Dopamine Epinephrine Glucagon Insulin	100 mL	150 mL over 15 min	Improved	Survived
[123]	Carvedilol	3.16	↓ BP	Dopamine Glucagon Insulin Norepinephrine	NR	NR	Improved	Survived
[127][a]	Labetalol Amlodipine	0.99 2.00	↓ BP CNS ↓ ↓ HR	Calcium Fluid resuscitation Insulin Norepinephrine		0.25 mg/kg/min over 3 h, then 0.167 mg/kg/min over 1.5 h	Improved	Survived
[111][a]	Metoprolol	−0.34	↓ BP CNS ↓ Cardiac arrest	Calcium ECMO Glucagon Insulin Norepinephrine Pacemaker	NR	NR	No response	Survived
[115]	Metoprolol	−0.34	CNS ↓ ↓ BP ↓ HR Cardiac arrest	Dobutamine ECMO Epinephrine Glucagon Insulin Norepinephrine Vasopressin	1.5 mL/kg	0.25 mL/kg over 30 min	Unclear	Survived
[124]	Metoprolol	−0.34	CNS ↓ ↓ BP ↓ HR Cardiac arrest	Atropine Bicarbonate Calcium Epinephrine Fluid resuscitation Glucagon Insulin	NR	NR	Improved	Survived
[126]	Nebivolol Baclofen Diazepam	0.94 −0.94 3.86	CNS ↓ ↓ BP ↓ HR Cardiac arrest	Calcium Epinephrine Fluid resuscitation Insulin	100 mL	1000 mL over 1 h	Improved	Survived
[112]	Metoprolol Bupropion	0.34 3.08	↓ HR ↓ BP Cardiac arrest	Calcium Catecholamines Fluid resuscitation Glucagon IABP Insulin	100 mL	Not given	Asystolic arrest 30 s after ILE	Died

(continued)

Table 6. Continued

Reference	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[118]	Propranolol Tramadol Zolpidem Alprazolam	0.99 0.40 2.35 2.50	CNS ↓ ↓ BP ↓ HR	Dobutamine ECMO Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine Vasopressin	1.5 mL/kg × 2	0.25 mL/kg/min	None	Died
[113]	Propranolol	0.99	CNS ↓ ↓ BP ↓ HR Seizure Cardiac arrest	Atropine Benzodiazepines Epinephrine Fluid resuscitation Glucagon Insulin Isoprenaline Phenytoin Pacemaker	100 mL	400 mL over 20 min	Improved	Survived
[116][a]	Propranolol Pentobarbital Detomidine Romifidine	0.99 2.04 2.37 0.32	CNS ↓ ↓ BP ↓ HR IVCD	Bicarbonate Calcium Glucagon Insulin	NR	NR	No response	Survived
[119][a]	Propranolol	0.99	↓ BP Seizure IVCD	Atropine Benzodiazepines Dopamine Fluid resuscitation Glucagon Insulin	100 mL	900 mL over 70 min	Improved	Survived
[120][a]	Propranolol Doxazosin	0.99 0.54	CNS ↓ ↓ BP ↓ HR	Epinephrine Glucagon Insulin Isoproterenol Norepinephrine Phenylephrine Vasopressin	NR	NR	No response	Survived
[123]	Propranolol	0.99	↓ BP Cardiac arrest	Atropine Bicarbonate Epinephrine Glucagon	NR	NR	Improved	Survived
[125]	Metoprolol Diltiazem	0.34 2.64	↓ BP CNS ↓	Calcium Fluid resuscitation Insulin	100 mL	1.5 L over 1 h	Improved	Survived
[128]	Metoprolol Imipramine	−0.34 2.07	↓ BP CNS ↓	Bicarbonate Calcium Glucagon Fluid resuscitation Insulin Norepinephrine	NR	400 mL/h over 2 h	Improved over 5 h	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

In a separate study, Perichon and colleagues administered verapamil via an orogastric tube to simulate the clinical overdose scenario. Each rat received an intravenous dose of either 0.2 mmol/kg calcium chloride, Hartmann's solution, or 20% ILE at an initial loading dose of 4 mL/kg over 10 min, followed by an infusion of 4 mL/kg/h. The ILE administration resulted in increased mortality compared to the other groups.[56] In a different rodent model of intravenous verapamil toxicity, Tebbutt and colleagues induced toxicity via an intravenous administration of verapamil. After toxicity was established, the investigators administered either ILE or 0.9% saline. The median lethal dose of verapamil was higher and a smaller decrease in heart rate was observed during verapamil infusion in ILE-treated animals compared with saline treatment.[57] Bania and colleagues induced verapamil toxicity in dogs through an intravenous infusion of the verapamil. Once the mean arterial pressure fell by 50% from its baseline, all dogs received atropine and calcium chloride. The dogs subsequently were randomized to receive ILE or an equivalent volume of 0.9% saline. ILE treated dogs sustained a higher MAP over time compared with the saline-treated animals. All seven ILE-treated animals survived, whereas only 1/7 saline-treated animals survived.[24]

Diphenhydramine

There are no controlled studies in humans evaluating ILE in the treatment of diphenhydramine toxicity. Table 8 summarizes the human case reports involving the use of ILE in the treatment of diphenhydramine toxicity.[166–170]

Varney and colleagues assessed the effects of ILE in acute diphenhydramine toxicity in a sedated and ventilated swine model.[60] The pigs were administered 1 mg/kg/min of

Table 7. Summary of human case reports involving calcium channel antagonists treated with ILE ($n = 42$).

Reference	Substance	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[134]	Amlodipine	2.00	"Unstable"	Calcium Dopamine ECMO Epinephrine Glucagon Insulin Methylene blue Norepinephrine Phenylephrine Vasopressin	100 mL	0.25 mL/kg over 1 h	Transient improved	Survived
[138][a]	Amlodipine Metoprolol Verapamil	2.00 −0.34 2.91	↓ BP ↓ HR Cardiac arrest	Atropine Calcium Dopamine Epinephrine Glucagon Insulin	1.5 mL/kg	0.25 mL/kg/min over 1 h	Improved	Survived
[143]	Amlodipine	2.00	↓ BP CNS ↓ ↓ HR	Calcium Dopamine Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine Terlipressin	250 mL	NR	Unclear response	Survived
[149][a]	Amlodipine Metoprolol	2.00 −0.34	↓ HR ↓ BP	Calcium Dobutamine Epinephrine Glucagon IABP Insulin Milrinone Pacemaker Phenylephrine Plasmapheresis	NR	NR	Not specified	Survived
[151]	Amlodipine	2.00	↓ BP	Calcium Glucagon Fluid resuscitation Glucagon Norepinephrine Phenylephrine Vasopressin	100 mL	2300 mL over 4.5 h	Improved	Survived
[154][a]	Amlodipine	2.00	↓ BP CNS ↓	Calcium Dopamine Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine Vasopressin	NR	NR	No response	Died
[157]	Amlodipine	2.00	CNS ↓ ↓ BP	Calcium Dopamine Fluid resuscitation Glucagon Insulin Norepinephrine Phenylephrine Vasopressin	1.5 mg/kg	0.25 mL/kg/h for unspecified duration	Unclear response	Survived
[158]	Amlodipine Metoprolol	2.00 −0.34	↓ BP ↓ HR	Calcium Dopamine Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine Vasopressin	120 mL × 2	6200 mL over 5 h	Transiently improved	Died
[160]	Amlodipine	2.00	↓ HR ↓ BP CNS ↓ Junctional rhythm	Calcium Insulin Norepinephrine	NR	NR	NR	Survived
[162]	Amlodipine Metformin	2.00 −0.34	CNS ↓ ↓ BP	Bicarbonate Calcium Glucagon Insulin L-carnitine Norepinephrine	120 mL × 2	NR	No response	Survived

(continued)

Table 7. Continued

Reference	Substance	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[127][a]	Amlodipine Labetalol	2.00 0.99	↓ BP CNS ↓ ↓ HR	Calcium Fluid resuscitation Insulin Norepinephrine	1.5 mL/kg	0.25 mg/kg/min over 3 h, then 0.167 mg/kg/min over 1.5 h	Improved	Survived
[163]	Amlodipine	2.00	↓ BP CNS ↓	Calcium Fluid resuscitation Insulin Phenylephrine Vasopressin	100 mL	2 L over 4.5 h	No response	Died
[133]	Diltiazem	2.64	↓ BP CNS ↓ ↓ HR	Calcium Epinephrine Fluid resuscitation Insulin	100 mL	0.25 mL/kg/h over 7 h	Improved 12 h after ILE bolus	Survived
[135]	Diltiazem	2.64	↓ BP	Calcium Dobutamine Fluid resuscitation Glucagon Norepinephrine	80 mL	500 mL over 30 min	Improved	Survived
[111][a]	Diltiazem Metoprolol	2.64 −0.34	↓ BP CNS ↓ Cardiac arrest	Calcium ECMO Glucagon Insulin Norepinephrine Pacemaker	NR	NR	No response	Survived
[112]	Diltiazem Propranolol	2.64 0.99	↓ BP ↓ HR	Atropine Calcium Dopamine Epinephrine IABP Insulin Pacemaker	150 mL	NR	Asystolic arrest within 30 s of ILE	Died
[136][a]	Diltiazem Amitriptyline	2.64 3.96	↓ BP CNS ↓ CHB	Atropine Bicarbonate Calcium Fluid resuscitation "Inotropic support"		500 mL over 30 min	Improved	Survived
[140]	Diltiazem	2.64	↓ BP CNS ↓	Calcium ECMO Glucagon Insulin "Vasopressors"	1/5 mL/kg	0.5 mL/hg/h for an unspecified duration	No response	Died
[152]	Diltiazem	2.64	↓ BP CNS ↓ ↓ HR	Atropine Bicarbonate Calcium Dobutamine Dopamine Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine	NR	0.5 mL/kg/h for an unspecified duration	Improved	Survived
[153]	Diltiazem	2.64	↓ BP	Calcium Fluid resuscitation Insulin Norepinephrine	1.5 mL/kg	0.25 mL/kg over 1 h	Improved	Survived
[155][a]	Diltiazem	2.64	↓ BP ↓ HR Seizure	Atropine Benzodiazepine Calcium Digoxin Epinephrine IABP Insulin Milrinone Norepinephrine Pacemaker Phenylephrine Vasopressin	1 mg/kg	0.05 mg/kg/min	Improved	Survived
[156]	Diltiazem Citalopram	2.64 0.41	↓ BP CNS ↓	Bicarbonate Epinephrine Fluid resuscitation Norepinephrine Vasopressin	1.5 mL/kg	1 L	Improved	Survived
[125]	Diltiazem Metoprolol	2.64 −0.34	↓ BP CNS ↓	Calcium Fluid resuscitation Insulin	100 mL	1.5 L over 1 h	Improved	Survived

(continued)

Table 7. Continued

Reference	Substance	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[164]	Diltiazem Bisoprolol	2.64 0.11	↓ BP ↓ HR	Calcium Dopamine Fluid resuscitation Glucagon Norepinephrine Vasopressin	1.5 mL/kg	6.5 mL/kg over 26 min	MAP Improved 8 mmHg post-infusion; vasopressors started to be weaned 4 h post-ILE	Survived
[132]	Felodipine	4.92	↓ BP ↓ HR CNS ↓	Calcium Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine	1.5 mL/kg	15 mL/kg/h over 50 min	Improved	Survived
[137][a]	Felodipine	4.92	"Vasoplegic shock," Abdominal compartment syndrome, Ischemic bowel	Calcium Glucagon Insulin MARS	NR	NR	No response	Died
[129][a]	Verapamil	2.91	CHB Cardiac arrest CNS ↓ ↓ BP	Calcium ECMO Fluid resuscitation Insulin Vasopressors	NR	NR	No change with ILE	Survived
[130]	Verapamil Trandolapril	2.91 XX	↓ BP ↓ HR	Calcium Dopamine Glucagon Insulin	NR	Infusion given; dose and duration not specified	No response	Survived
[131]	Verapamil	2.91	↓ BP Cardiac arrest	Fluid resuscitation Norepinephrine	1.5 mL/kg	0.25 mL/kg/min over 1 h	Unclear response	Survived
[114][a]	Verapamil Beta blocker	2.91	↓ BP	Calcium Dopamine Fluid resuscitation IABP Insulin Norepinephrine Pacemaker	1.5 mL/kg	0.25 mL/kg/min for 30 min and restarted later for another 60 min	Transiently improved	Died
[139]	Verapamil	2.91	↓ BP	Calcium Dopamine Glucagon Norepinephrine	100 mL	0.5 mL/kg/h over 8 h	Weaned vasopressors 3.5 h later	Survived
[141]	Verapamil	2.91	↓ BP CHB	Atropine Calcium Dopamine Epinephrine Glucagon Insulin Norepinephrine Phenylephrine Pacemaker	100 mL × 3	500 mL over 30 min; later 150 mL over 15 min	No response	Survived
[142][a]	Verapamil	2.91	↓ HR ↓ BP CNS ↓ CHB	Calcium Dopamine Epinephrine Fluid resuscitation Insulin Isoproterenol Nitrous oxide Norepinephrine Pacemaker Vasopressin	100 mL given twice	500 mL over 30 min	Improved	Survived
[144][a]	Verapamil	2.91	↓ BP	Atropine Calcium Fluid resuscitation Insulin Norepinephrine Phenylephrine	1.5 mg/kg	NR	No change with ILE	Survived
[146][a]	Verapamil	2.91	↓ BP CNS ↓	Calcium Dopamine Fluid resuscitation Glucagon	500 mL	NR	Improved in 20 min	Survived
[146]	Verapamil	2.91	↓ BP CNS ↓	Calcium Dopamine	500 mL	NR	Improved in 1 h	Survived

(continued)

Table 7. Continued

Reference	Substance	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[147][a]	Verapamil DPH	2.91 1.92	↓ HR ↓ BP CNS ↓	Atropine Calcium ECMO Epinephrine Glucagon Insulin Methylene blue Norepinephrine Pacemaker Vasopressin		960 mL	No response	Survived
[148]	Verapamil	2.91	↓ BP	Bicarbonate Calcium Dopamine Epinephrine Fluid resuscitation Glucagon Insulin Isoproterenol Norepinephrine	100 mL	4700 mL over 7 days	Vasopressors weaned 3 h later	Survived
[150]	Verapamil	2.91	↓ HR ↓ BP	Calcium ECMO Epinephrine Fluid resuscitation Norepinephrine Pacemaker Plasmapheresis	100 mL	0.2 mL/kg/min over 4 h	No change with ILE	Survived
[159][a]	Verapamil	2.91	↓ BP	Norepinephrine	NR	NR	No response	Died
[161]	Verapamil	2.91	CNS ↓ ↓ BP	Calcium Epinephrine Fluid resuscitation Glucagon Insulin Norepinephrine Vasopressin Phenylephrine	200 mL	NR	No response	Survived
[165]	Verapamil	2.91	↓ BP CNS ↓	Calcium Glucagon Fluid resuscitation Norepinephrine	100 mL	0.5 mL/kg/h over 23 h	Improved after unspecified time	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

diphenhydramine intravenously until the mean arterial pressure was 60% of its baseline. There was no difference in overall survival or time to death in the two groups (11/12 animals treated with 20% ILE died with a mean time to death of 12 min 33 s versus 10/12 with 7 mL/kg bolus sodium bicarbonate plus infusion of 0.25 mL/kg with a mean of 7 min 48 s). The authors state there were transient differences in continuous heart rate favoring bicarbonate, and blood pressure favoring ILE.

Sedative hypnotics and anesthetics

Common gamma-aminobutyric acid (GABA) agonists include barbiturates, baclofen, propofol, and benzodiazepines. There are no human controlled studies evaluating ILE for the treatment of GABA agonist toxicity. A single randomized human trial evaluated the impact of ILE on recovery time and quality of recovery in 66 patients receiving isoflurane anesthesia for a laparoscopic cholecystectomy.[16] The ILE group, received 2 mL/kg of 30% ILE (Fat Emulsion Injection (C14–24); Sino-Swed Pharmaceutical Corp. Ltd., Wuxi, China) at the completion of skin closure along with discontinuation of isoflurane. This group of patients experienced a more rapid recovery and had better perceived quality of recovery than the control group who did not receive ILE. The time to eye opening was shorter in the ILE group than in the controls (median of 15.5 and 20.0 min respectively, $p = 0.01$). The ILE group was extubated earlier (17 versus 21 min). ILE treated patients also achieved faster onset of a Modified Aldrete Post-Anesthesia Recovery (MAPAR) score of at least 9 (which is used to determine safe discharge from the post-anesthesia care unit) than control patients (median time 28.5 versus 33.6 min). However, neither of these later measurements was statistically significant. This well-designed study reports that a single dose of 2 mL/kg of ILE significantly decreased the recovery time by 4.5 min and post-operative perceived quality of anaesthesia after isoflurane general anaesthesia. As this study involved therapeutic administration of an inhaled anesthetic uncertainty remains as to its validity in poisoning scenarios (Table 1).

Table 9 summarizes the human case reports involving the use of ILE in the treatment of GABA agonist toxicity.[171,172]

In animal studies, thiopental is the most commonly studied barbiturate examining ILE effectiveness. In a rabbit model, animals received either 4 mL/kg 0.9% saline or 20% ILE immediately after an IV dose of 20 mg/kg thiopental.[47] The

Table 8. Summary of human case reports involving diphenhydramine (DPH) treated with ILE ($n = 5$).

Reference	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[166]	1.92	↓ BP CNS ↓ WCT Seizure Cardiac arrest	Amiodarone Benzodiazepine Bicarbonate Epinephrine Fluid resuscitation Norepinephrine Phenylephrine	1.5 mL/kg	0.25 mL/kg/min over 26 min	Improved	Survived
[167]	1.92	↓ BP CNS ↓ WCT	Bicarbonate Calcium Fluid resuscitation Magnesium	1.5 mL/kg × 2	NR	Improved	Survived
[168]	1.92	↓ BP CNS ↓ Cardiac arrest	Atropine Bicarbonate Dopamine Epinephrine	60 mL	NR	Improved transiently	Died
[169]	1.92	"Signs of cardiotoxicity" WCT	Bicarbonate Hypertonic saline	100 mL	0.25 mL/kg/min (duration not specified)	NR	Survived
[170]	1.92	CNS ↓ ↑ HR Status epilepticus ↓ BP WCT Cardiac arrest	Amiodarone Benzodiazepine Bicarbonate Epinephrine Lidocaine Norepinephrine Vasopressin	1.5 mL/kg	0.25 mL/kg/min over 1 h	Improved	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↑ HR: tachycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references: [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

Table 9. Summary of human case reports involving GABA agonists treated with ILE ($n = 2$).

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[172][a]	Baclofen	−0.94	↓ BP CNS ↓	Fluid resuscitation	1.5 mL/kg	0.25 mL/kg/min over 30 min	Improved over 2 h	Survived
[171][a]	Pentobarbital Phenytoin	−0.94 2.52	Cardiac arrest	NR	1.5 mL/kg	NR	Improved	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

investigators employed bispectral index (BIS) monitoring to determine the depth of anesthesia. The BIS was higher in the saline group, suggesting lighter level of sedation, but there was no difference in the duration of anesthesia. The authors concluded that ILE increases CNS depression in the early distribution phase after lipophilic anesthetic administration. In a rodent study involving administration of ILE after the intravenous administration of pentobarbital, an increased duration of sleep was observed in rats treated with 10% ILE (87 versus 177 min).[46]

A single rat study randomized 40 animals to either 0.5 or 2.0 mL of 30% ILE or an equivalent volume of 0.9% saline following etomidate-induced loss of righting reflex.[63] The 2 mL dose of ILE significantly shortened both the duration of loss of righting reflex (from 755 ± 64 s to 493 ± 27 s) and the time to return to normal activities (1104 ± 114 s to 643 ± 36 s). They also demonstrated partitioning of the etomidate out of the aqueous phase of the serum. The 0.5 mL dose had no effect.

There are currently no controlled studies in humans involving baclofen, although several case reports involving both humans [172] and animals [64,70,78] are published. A non-randomized retrospective review of five dogs and cats with baclofen poisoning reported improved hemodynamics over an unclear time course following the administration of ILE.[78] As details of ILE administration were not specified, ascertaining a temporal relationship between treatment and response is difficult. Utilizing a rodent model, Gragasin induced intra-arterial vasoconstriction via the administration of phenylephrine, followed by vasodilation with the use of an intra-arterial propofol infusion. The addition of progressively increasing doses of ILE was associated with greater reversal of propofol vasodilation.[38]

Tricyclic antidepressants

There was one RCT examining the efficacy of ILE on duration of cardiotoxicity and subsequent complications of severe tricyclic antidepressant (TCA) toxicity, which was published only in conference proceedings and not available through traditional search methods.[15] This study included a total of 108 patients randomized to either receive standard treatment with bicarbonate ($n = 54$) or standard treatment plus intravenous lipid emulsion ($n = 54$). No statistically significant difference was observed between the groups concerning the time needed for ECG reversal (despite being 20 minutes shorter in the ILE group), in blood pressure at the time of ECG reversal, in mortality (1/54 in controls versus 0/54 in ILE group) or in length of hospitalization. The authors concluded that there was not any significant

Table 10. Summary of human case reports involving cyclic antidepressant toxicity treated with ILE ($n = 22$).

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[175][a]	Amitriptyline	3.96	CNS ↓ WCT	Bicarbonate Fluid resuscitation Norepinephrine Phenylephrine	100 mL	0.25 mL/kg/min	Improved	Survived
[178]	Amitriptyline Liraglutide	3.96	↓ BP CNS ↓ Seizure Cardiac arrest	Benzodiazepine Bicarbonate Calcium Glucagon	100 mL	NR	Improved	Survived
[179]	Amitriptyline	3.96	CNS ↓ Seizure WCT ↓ BP Cardiac arrest	Bicarbonate Dobutamine Dopamine Epinephrine Norepinephrine Pacemaker Plasmapheresis	1.5 mL/kg	0.25 mL/kg/min over 4 h	Improved	Survived
[180]	Amitriptyline	3.96	CNS ↓ Seizure WCT Cardiac arrest	Bicarbonate Epinephrine Norepinephrine	100 mL	400 mL over 30 min	Improved	Survived
[181]	Amitriptyline	3.96	CNS ↓ Seizure WCT ↓ BP	Bicarbonate Benzodiazepines Fluid resuscitation Metaraminol	100 mL	400 mL over 30 min	Improved	Survived
[182]	Amitriptyline	3.96	CNS ↓ Seizure WCT ↓ BP	Benzodiazepines Bicarbonate Fluid resuscitation Epinephrine	100 mL	400 mL over 15 min	Improved	Survived
[184]	Amitriptyline	3.96	CNS ↓	Bicarbonate Epinephrine Vasopressin	250 mL of 10% given twice	250 mL/h for 4 h	Return of spontaneous circulation	Survival
[186]	Amitriptyline	3.96	CNS ↓ Seizure WCT Cardiac arrest	Bicarbonate Calcium Epinephrine Hypertonic saline Lidocaine Magnesium Norepinephrine	150 mL, later 40 mL	16 mL/h over 36 h	No response	Survived
[187]	Amitriptyline	3.96	CNS ↓ ↓ BP Seizure WCT Cardiac arrest	Benzodiazpine Bicarbonate Epinephrine Magnesium	1.5 mL/kg × 2	0.25 mL/kg/min over 30 min	Improved	Survived
[189]	Amitriptyline Citalopram	3.96	CNS ↓ Seizure WCT ↓ BP Cardiac arrest	Bicarbonate Epinephrine "Inotropes" Lignocaine Standard ALS guidelines"	1.5 mL/kg	0.25 mL/kg/min over 1 h	Improved	Survived
[169]	Amitriptyline DPH	3.96 1.92	"Signs of cardiotoxicity" WCT	Bicarbonate Hypertonic saline	100 mL	0.25 mL/kg/min (duration not specified)	NR	Survived
[176]	Dothiepin	2.92	↓ BP CNS ↓ WCT Cardiac arrest	Amiodarone Bicarbonate Dobutamine Fluid resuscitation Pacermaker Vasopressors	1.5 mL/kg	0.25 mL/kg/min over 15 min	Improved	Survived
[177]	Dosulepin	2.92	Seizure CNS ↓ WCT	Bicarbonate Benzodiazepine Fluid resuscitation	1.5 mL/kg	400 mL over 20 min	Improved	Survived
[191][a]	Doxepin	2.93	↓ BP CNS ↓ WCT	Bicarbonate Dopamine Fluid resuscitation Lidocaine Magnesium Norepinephrine Vasopressin	275 mL over 90 min	275 mL over 90 min	Unclear	Survived
[183]	Dothiepin	2.92	CNS ↓ Seizure ↓ BP WCT	Bicarbonate Thiopentone	1 mL/kg	0.25 mL/kg/min over 1 h	Improved	Survived
[185][a]	Doxepin	2.93	CNS ↓ Seizure WCT	Bicarbonate Benzodiazepine Hypertonic saline	100 mL × 2	0.25 mL/kg/min × 6 h	Unclear	Survived

(continued)

Table 10. Continued

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[188][a]	Doxepin	2.93	CNS ↓ Seizure WCT Cardiac arrest	Amiodarone Bicarbonate Benzodiazepine Epinephrine Fluid resuscitation Fosphenytoin Norepinephrine	1.5 mL/kg × 2	0.25 mL/kg/min over 1 h	Improved	Survived
[190]	Doxepin	2.93	CNS ↓ Seizure ↓ BP WCT	Bicarbonate Benzodiazepine Levetiracetam Phenobarbital	1.5 mL/kg	0.25 mL/kg/min over 2 h	Improved	Survived
[174]	Imipramine	2.07	CNS ↓ WCT ↓ BP Seizure Heart block	Bicarbonate Hypertonic saline "Vasopressors"	100 mL × 2	0.25 mL/kg/min over 30 min	Improved transiently	Survived
[185]	Imipramine	2.07	WCT Seizure ↓ BP	Benzodiazpine Bicarbonate Hypertonic saline "Vasopressors"	100 mL × 2	0.25 mL/kg/min over 6 h	Improved over 4 h	Survived
[128]	Imipramine Metoprolol	2.07 −0.34	↓ BP CNS ↓	Bicarbonate Calcium Glucagon Fluid resuscitation Insulin Norepinephrine	NR	400 mL/h over 2 h	Improved over 5 h	Survived
[173]	"TCA"		CNS ↓ Seizure WCT Cardiac arrest	Bicarbonate	250 mL	100 mL/h over 24 h	Improved transiently	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

change in outcomes in patients receiving ILE. Nevertheless, the quality of evidence could not be fully assessed since the complete article is still not published (Table 1). Table 10 summarizes the human case reports involving the use of ILE in the treatment of TCAs.[110,128, 169,173–190]

Numerous animal studies evaluated the role of ILE in the treatment of TCA toxicity. Amitriptyline and clomipramine are the most widely studied substances. The use of ILE resulted in improvement of hypotension in all three clomipramine studies,[39,40,62] and survival increased in two.[39,62] One study found lower mortality with ILE-treated rabbits compared with sodium bicarbonate.[39] Another clomipramine study examined 0.9% saline, sodium bicarbonate, 20% ILE, or ILE plus an unspecified number of plasma exchange cycles for each animal. The median survival was 12 min in the control group, compared with 30 min in the bicarbonate group, 85 min in the ILE group, and 90 min in the ILE with cycled plasma exchange group.[42]

The effect of ILE on clomipramine toxicity was studied in 20 rabbits. Animals received either 12 mL/kg of 20% ILE or 0.9% saline once intravenous clomipramine infusion reduced MAP by 50%.[40] The MAP was 10 mmHg higher immediately after ILE administration compared to controls, although this effect decreased over time. ILE treatment was associated with higher serum clomipramine concentration and a lower volume of distribution than control animals (5.7 L/kg in the lipid group versus 15.9 L/kg in the saline group). The authors concluded that these data support the "lipid sink" hypothesis.

In a separate rabbit model of intravenous clomipramine toxicity, Cave randomized 15 animals to receive 3 mL/kg of 8.4% sodium bicarbonate, 3 mL/kg of 20% ILE, or 24 mg/kg of liposome-like lipid dispersions 10 min after the onset of toxicity (defined as a 50% reduction in MAP). At 30 min post-treatment, the MAP was highest in the ILE-treated animals (61 mmHg), compared with 43 mmHg in the liposome-like lipid dispersion group, and 10 mmHg in the sodium bicarbonate group. All of the ILE and liposomal-like lipid dispersion treated animals and two of five bicarbonate-treated animals survived to 30 min.[31]

The effects of ILE in treatment of amitriptyline toxicity in animal experiments differ significantly from clomipramine. Some of this difference may be accounted for by differences in the models utilized. Four experiments assessed the role of ILE in amitriptyline toxicity. Two studies found ILE sequesters amitriptyline in plasma, but had no significant effect on hemodynamic parameters.[45,48] One rodent model that administered 70 mg/kg amitriptyline orogastrically, compared 4 mL/kg 20% ILE with 4 mL/kg Hartmann's solution and 4 mL/kg of 8.4% hypertonic sodium bicarbonate. Survival was significantly lower with ILE treatment (10% ILE versus 70% for the other two groups) and blood amitriptyline concentration was higher with ILE treatment.[55] Finally, in a swine model of intravenous amitriptyline toxicity, a 7 mL/kg loading dose and 0.25 mL/kg/min infusion of an unspecified concentration ILE was compared with 2 mL/kg loading-dose and 0.25 mL/kg/min infusion of hypertonic sodium bicarbonate. The median time from hypotension to death was prolonged with bicarbonate therapy (10 min [IQR 6–61] versus 5 min [IQR 4.5–6] for ILE), but neither treatment ultimately affected overall survival.[61]

Table 11. Summary of human cases of non-cyclic antidepressant/antipsychotics toxicity treated with ILE ($n = 21$).

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[204]	Bupropion	3.08	Seizure ↑ HR CNS ↓	Benzodiazepine Dopamine Epinephrine ECMO Fluid resuscitation Norepinephrine Phenytoin	NR	20 mL/kg given. No concentration or rate specified	NR	Survived
[199]	Bupropion	3.08	Seizure ↑ HR CNS ↓ IVCD ↓ BP	Bicarbonate Calcium Dopamine Fluid resuscitation Glucagon Lidocaine Norepinephrine Lidocaine	1.5 mL/kg × 2	0.25 mL/kg/min over 1 h	Improved transiently	Survived
[22]	Bupropion	3.08	Seizure ↓ BP	NR	NR	NR	NR	Survived
[196]	Bupropion	3.08	Seizure CNS ↓ ↓ BP	Benzodiazepine Bicarbonate Epinephrine	100 mL × 2	46 mL/kg over 12 h	Improved	Survived
[102]	Bupropion Lamotrigine	3.08 0.19	Seizure CNS ↓ WCT Cardiac arrest	Amiodarone Bicarbonate Calcium Epinephrine Norepinephrine Vasopressin	100 mL	NR	Improved	Survived
[205][a]	Bupropion	3.08	Seizure CNS ↓ ↓ BP ↓ HR WCT Cardiac arrest	Plasmapheresis	140 mL	800 mL over 4 h	Improved	Survived
[189]	Amitriptyline Citalopram	3.96 0.41	CNS ↓ Seizure WCT ↓ BP Cardiac arrest	Bicarbonate Epinephrine "Inotropes" Lignocaine Standard ALS guidelines"	1.5 mL/kg	0.25 mL/kg/min over 1 h	Improved	Survived
[195]	Haloperidol Dexmedetomidine	2.80 2.85	Cardiac arrest	Amiodarone	NR	NR	Improved	Survived
[206]	Haloperidol	2.80	Chest pain Cardiac arrest	Amiodarone Atropine Epinephrine	250 mL	NR	Improved	Survived
[201]	Olanzapine Citalopram	3.20 0.41	IVCD Seizure ↓ BP ↓ HR	Bicarbonate Dopamine Epinephrine Isoproterenol Levetiracetam Pacemaker	NR	21 mL/h (10% ILE). Later 0.005 mL/kg/min (20%ILE) × 17 h	No response	Survived
[202]	Olanzapine	3.20	↑ HR CNS ↓	IVF	1.5 mL/kg × 2	0.25 mL/kg/min of unknown duration	Improved transiently	Survived
[207]	Olanzapine	3.20	CNS ↓	NR	NR	100 mL over 15 min; later additional 100 mL over 30 min	Improved	Survived
[192]	Quetiapine	1.82	↑ HR CNS ↓ ↓ BP	Fluid resuscitation	1.5 mL/kg × 2	NR	Improved	Survived
[194]	Quetiapine	1.82	↑ HR CNS ↓ ↓ BP	Bicarbonate Epinephrine Fluid resuscitation Norepinephrine Phenylephrine	100 mL	500 mL over 1 h	Improved	Survived
[198]	Quetiapine Sertraline	1.82 2.39	CNS ↓ ↓ BP	None	100 mL	400 mL over 1 h	Improved	Survived
[197]	Quetiapine Desvenlafaxine Bupropion Escitalopram	1.82 0.89 3.08 0.41	↑ HR CNS ↓ ↓ BP Cardiac arrest	Bicarbonate Fluid resuscitation Norepinephrine	1.5 mL/kg	0.25 mL/kg/min over 2.5 h	Improved transiently	Died
[200][a]	Quetiapine	1.82	↑ HR CNS ↓ ↓ BP	NR	100 mL 1 h	420 mL over 1 h	Improved transiently	Survived
[98]	Venlafaxine Lamotrigine Diazepam	0.70 −0.19 3.86	CNS ↓ Seizure Serotonin syndrome	Benzodiazepines Fluid resuscitation	2.5 mL/kg	NR	Improved	Survived

(continued)

Table 11. Continued

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[145]	Zopiclone Venlafaxine	XX 0.70	CNS ↓ ↓ BP	Fluid resuscitation	100 mL	400 mL over 40 min	Improved	Survived
[203]	Venlafaxine Amitriptyline Citalopram	0.70 3.96 0.41	CNS ↓ ↓ BP	Bicarbonate Isoproterenol Pacemaker	500 mL	NR	Improved	Survived
[193][a]	Zolpidem Venlafaxine	2.35 0.70	CNS ↓ ↓ BP	Benzodiazepine Fluid resuscitation	150 mL	NR	Improved	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ECMO: Extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

In a swine model of desipramine toxicity, the investigators compared the effect of 20% ILE to various resuscitative interventions with or without ILE.[52] There were seven pigs per group. ILE was administered as a loading-dose of 2 mL/kg over 2–3 min, followed by a continuous infusion (0.25 mL/kg/min) for 10 min. Vasopressin administered as a single agent resulted in 100% survival. This regimen compares with 71% survival in the vasopressin with ILE group, 57% in the vasopressin with epinephrine and ILE, 29% in the ILE only group, 14% in the epinephrine only group, 14% in the epinephrine with vasopressin, and 0% in the epinephrine with ILE group and the control group (cardiopulmonary resuscitation only).

Non-cyclic antidepressant and psychiatric medications

There are no randomized controlled studies assessing the effect of ILE in human toxicity due to antipsychotic and non-TCA medications. Downes conducted a single retrospective review of human cases receiving ILE for sedative hypnotic overdose, including six cases of quetiapine overdose.[9] There was no benefit observed from ILE administration in these cases. Table 11 summarizes the human case reports involving the use of ILE in the treatment of non-cyclic antidepressant and miscellaneous psychiatric medications.[22,98,102,145,189,192–207]

A controlled animal study evaluated the effects of ILE on haloperidol-induced neurotoxicity in rabbits.[50] Following the administration of 2.6 mg/kg haloperidol, rabbits received doses of 6, 12, or 18 mL/kg of 20% ILE or a control of 0.9% saline. Haloperidol treated rabbits developed hypotension, miosis, and problems with positioning and balance. While ILE was associated with minor improvements in motor function, it was also associated with a significant increase in mortality.

Miscellaneous drugs

Various case reports describe the use of ILE for the treatment of numerous toxicities (Table 12).[145,193,195,208–218]

An animal experiment failed to find benefit for ILE in the management of intravenous digoxin toxicity.[26] A rodent experiment examined the effect of ILE in tramadol overdose. Animals all received 50 mg/kg of tramadol intravenously. At an ILE dose of 6 and 12 mL/kg survival was seen in 5/5 animals. At an ILE dose of 18 mg/kg survival was seen in 4/5 animals. These results were statistically significant compared to saline controls, in which 3/5 animals receiving 18 mL/kg saline survived.[59]

Assessment of the quality of evidence

Table 1 shows the summary estimates with associated Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings for human controlled studies reporting the effect of ILE on non-LA toxicity. All other evidence was rated as very low-quality evidence; the remaining human studies included in the systematic review were seriously limited by their study designs (all uncontrolled studies preventing comparison with a control group, such as case series and case reports) and by the high likelihood of publication bias (especially with case reports), while animal studies were seriously limited by indirectness (resuscitation model lacking generalizability to human poisoning clinical scenario) and significant imprecision (generally underpowered studies).

Discussion

In this systematic review of animal and human studies and reports on the effect of ILE in the context of acute intoxication with non-LA, we identified human and animal studies and case reports only yielding a low or very low quality of the evidence. Indeed, most randomized studies were conducted in the animal setting while human publications were almost exclusively case reports. Thus, the evidence available remains of low to very low quality. Most case reports also use several other treatments, which preclude the assessment of the singular effect of ILE. The amount of lipid given, the type of formulation used, the timing of administration with regards to the other treatments received as well as the rate of administration (bolus versus infusion) are heterogeneous thus reflecting a great variability in practice with regards to the use of this therapy.

This manuscript only focused on non-LA xenobiotics; a review of ILE for LA is published in a separate manuscript.[219] Nonetheless, when comparing the efficacy of ILE for lipophilic drugs, it is important to note a significant difference between LA and non-LA drugs. LA are generally administered parenterally, whereas non-LA are generally administered orally. It is unclear if this difference in route of administration affects reported efficacy of ILE.

Limitations

This systematic review has some limitations that should be noted. First, we performed a very broad search of the literature using sensible eligibility criteria by considering all types of study design, including animal studies to the exception of those in

Table 12. Summary of human case reports involving miscellaneous substances treated with ILE ($n = 15$).

References	Drug	Log D^b	Symptoms	Other treatment	ILE bolus dose	ILE infusion dose	ILE effect	Outcome
[209][a]	Bromadiolone	3.86	Hepatic failure Coagulopathy	FFP Vitamin K	NR	1.5 mL/kg over 30 min, repeated 4 h later	Unclear	Survived
[215][a]	Caffeine	−0.088	CNS ↓ ↓ BP WCT	Amiodarone Epinephrine Norepinephrine	NR	565 mL over 2 h	Unclear	Survived
[210]	Chloroquine	1.15	↓ BP CNS ↓ Cardiac arrest	ECMO Fluid resuscitation	1.5 mL/kg	0.25 mL/kg/min for unspecified duration	Improved transiently	Survived
[208]	Cocaine	1.14	CNS ↓ Seizure ↑ HR	Bicarbonate Norepinephrine Phenytoin Thiopentone	100 mL	NR	Improved	Survived
[211]	Cocaine	1.14	CNS ↓ WCT ↓ BP	Bicarbonate	1.5 mL/kg	15 mL/kg/h × 15 min	Improved	Survived
[212]	Cocaine	1.14	CNS ↓ WCT Seizure	Benzodiazepine Bicarbonate Fluid resuscitation	1.5mL/kg × 2	0.25 mL/kg/min over 10 min. Repeated next day with 30 min infusion	No response	Died
[217]	Cocaine	1.14	Dyskinesia Ballismus		100mL	NR	Improved	Survived
[195]	Haloperidol Dexmedetom-idine	2.80 2.85	Cardiac arrest	Amiodarone	NR	NR	Improved	Survived
[214][a]	Hydrocarbon		CNS ↓ WCT	NR	100 mL × 2	0.25 mg/kg/min over 3 h	Improved over 3 h	Survived
[216][a]	Hydroxy-chloroquine	1.08	↓ BP CNS ↓ Cardiac arrest	Epinephrine Vasopressin	100 mL	900 mL over 30 min	Improved	Survived
[218]	Hydroxy-chloroquine	1.08	↓ BP IVCD Cardiac arrest	Benzodizaepine Bicarbonate Epinephrine Fluid resuscitation Pacemaker	100 mL	NR	No response	Died
[218]	Hydroxy-chloroquine	1.08	↓ BP IVCD CNS ↓ Cardiac arrest	Benzodiazepine Bicarbonate Epinephrine Fluid resuscitation	100 mL (10%)	400 mL (10%) over 30 min	No response	Died
[213][a]	Metformin	−5.44	Lactic acidosis	Bicarbonate Epinephrine Norepinephrine "THAM" Vasopressin	1.5 mL/kg	0.25 mL/kg/min over 30 min	No response	Died
[145]	Zopiclone Venlafaxine	XX 0.70	CNS ↓ ↓ BP	Fluid resuscitation	100 mL	400 mL over 40 min	Improved	Survived
[193][a]	Zolpidem Venlafaxine	2.35 0.70	CNS ↓ ↓ BP	Benzodiazepine Fluid resuscitation	150 mL	NR	Improved	Survived

ADR: Adverse drug effects; ↓ BP: hypotension; ↓ HR: bradycardia; CNS ↓: central nervous system depression; ILE: intravenous lipid emulsion; IVCD: Intraventricular conduction delay; NR: Not reported; WCT: Wide complex tachycardia.
[a]Abstract only.
[b]Adapted from references [220,221]. The log *D* refers to the logarithm of octanol/water partion coefficient.

which the ILE was administered *before or at the same time as* the toxic substance, as those models cannot be generalizable to human poisoning scenarios. The consideration of animal studies to support clinical practice may be perceived as not being appropriate by some. Our decision to consider such methodology was to ensure all possible studies examining ILE effects in poisoning were included. While results of animal studies may not be entirely generalizable to humans, such studies offer a better understanding of the underlying mechanisms of action and potential effects of ILE. Conversely, other than one RCT in lipophilic drug overdose, one RCT in reversal of sedation after therapeutic isoflurane anesthesia, one RCT in TCA toxicity, and one observational study in acute glyphosate toxicity, all human data extracted in our systematic review were derived from case series and case reports. In most of these cases, the authors felt that reversal of drug toxicity was related to ILE administration. In many cases, uncertainty exists as to the effect of ILE given the delay between the time ILE of administration and reported clinical improvement. Third, the presence of publication bias is very likely considering the significant proportion of the retrieved literature being case reports. Indeed, case studies reporting a positive response to an experimental treatment such as ILE are more likely to be published than those in which the treatment failed. The cases described were also very heterogeneous. Many substances were involved often in mixed drug or chemical ingestions. The severity of symptoms and signs varied from case to case as well as the threshold for ILE administration. ILE dose was inconsistent, and many other treatments had been implemented prior to ILE administration. Also, most cases failed to confirm drug exposure or measure serum or blood drug concentrations before or after ILE administration. However, we could not explore the potential impact of these discrepancies in the effect of the intervention. Due to inherent inconsistencies in describing case reports, some information was not available to permit direct comparisons between various publications involving the same toxin.

Conclusion

The Clinical Toxicology's lipid emulsion collaborative workgroup was created to review all appropriate evidence pertaining to the use of ILE in clinical toxicology. This manuscript summarizes the findings of ILE as it relates to non-local anesthetic substance toxicity. Despite use of ILE for multiple substances in medical toxicology, the effect of ILE in various non-local anesthetic poisonings is heterogenous and the quality of evidence remains low to very low.

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Appendix

Medline (Ovid) search strategy for lipid emulsion therapy effect

(1) exp Fat Emulsions, Intravenous/
(2) lipid rescue.ti,ab,kw.
(3) (lipid adj3 emulsi*).mp.
(4) (fat adj3 emulsi*).mp.
(5) ((lipid or fat*) adj5 bolus).mp.
(6) (lipid adj3 (resuscitat* or therap* or infus*)).mp.
(7) (ILE adj5 (lipid* or emulsi* or fat*)).mp.
(8) (IFE adj5 (lipid* or emulsi* or fat*)).mp.
(9) (lipid adj3 sink*).mp.
(10) (lipid adj3 sequest*).mp.
(11) intravenous* lipid*.ti,ab,kw.
(12) intralipid*.mp.
(13) or/1-12
(14) exp Cardiovascular Agents/
(15) exp Sodium Channel Blockers/
(16) exp Calcium Channel Blockers/
(17) exp Adrenergic beta-Antagonists/
(18) ((sodium or Na*) adj3 channel block*).ti,ab,kw.
(19) ((calcium or Ca*) adj3 channel block*).ti,ab,kw.
(20) (beta adj3 block*).ti,ab,kw.
(21) B-blocker.ti,ab,kw.
(22) exp Central Nervous System Depressants/
(23) exp Psychotropic Drugs/
(24) exp Anti-Arrhythmia Agents/
(25) local an?esthetic*.mp.
(26) exp Amitriptyline/
(27) amitriptyline.mp.
(28) exp Bupropion/
(29) bupropion.mp.
(30) exp Chloroquine/
(31) chloroquine.mp.
(32) chlorpromazine.mp.
(33) clomipramine.mp.
(34) cocaine.mp.
(35) exp Dothiepin/
(36) (dosulepin or dothiepin).mp.
(37) glyphosate.mp.
(38) haloperidol.mp.
(39) lamotrigine.mp.
(40) olanzapine.mp.
(41) propofol.mp.
(42) quetiapine.mp.
(43) exp Sertraline/
(44) sertraline.ti,ab,kw.
(45) zopiclone.mp.
(46) ropivacaine.mp.
(47) levobupivacaine.mp.
(48) lignocaine.mp.
(49) diazepam.mp.
(50) exp Carnitine/
(51) carnitine.ti,ab,kw.
(52) exp Poisoning/
(53) poison*.ti,ab,kw.
(54) exp Noxae/ae, po
(55) po.fs.
(56) ae.fs.
(57) to.fs.
(58) exp Street Drugs/
(59) (lipophilic adj3 (drug* or toxin*)).ti,ab,kw.
(60) overdos*.ti,ab,kw.
(61) exp Antidotes/
(62) antidote*.ti,ab,kw.
(63) (toxic* or intoxic* or pharmacotoxic*).ti,ab,kw.
(64) Resuscitation/
(65) resuscitat*.ti,ab,kw.
(66) or/14-65
(67) 13 and 66