LIPAEMIC Report: Results of Clinical Use of Intravenous Lipid Emulsion in Drug Toxicity Reported to an Online Lipid Registry

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Abstract The use of intravenous lipid emulsion (ILE) as an antidote has prompted significant academic and clinical interest. Between August 2009 and August 2012, data from cases of ILE use in intoxicated patients in different hospitals on different continents were voluntarily entered into a registry based on the world wide web (www.lipidregistry.org). Here, we report data from this project. Participating centers were given access to the registry following institutional subscription. Specifically sought were details of the individual patients' presenting condition, indications for ILE use, ILE administration regimen, potential complications, and of clinical outcome. Forty-eight uses of ILE were reported from 61 participating centers. Ten cases of local anesthetic systemic toxicity were reported; all (10/10) survived. Thirty-eight cases of intoxication by other agents were reported [30

decreased conscious state, 8 cardiovascular collapse (3 deaths)]. There was an elevation in GCS ($p<0.0001$) and increased systolic blood pressure ($p=0.012$) from immediately prior to ILE administration to 30 min after use. One serious and two minor adverse effects of ILE use were recorded in 48 reported cases (one case of bronchospastic reaction, one case of hyperamylasemia and one case of interference with laboratory testing). In this series of cases reported to the registry, improvements were seen for GCS in patients with central nervous system toxicity and in systolic blood pressure in shocked patients over a short time frame after the injection of ILE. Few adverse effects were recorded. Clinical trials and the reporting of drug concentrations after ILE use are necessary to further elucidate the role of ILE in clinical toxicology.

Keywords Lipid emulsion · Registry · Antidote · Poisoning

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Introduction

Intravenous lipid emulsion (ILE) was first documented to be effective in animal models of intoxication by bupivacaine in 1998 [1]. Additional animal studies, coupled with positive outcomes following ILE use in humans [2–5], have subsequently led to clinical recommendation for ILE use in local anesthetic overdose [6, 7]. The success and safety of lipid resuscitation in this context, combined with a paucity of alternative antidotes, has seen ILE become firmly established as the antidote of choice for local anesthetic systemic toxicity (LAST).

Several mechanisms of action have been proposed to explain the beneficial effects of ILE in LAST. Proposed pharmacokinetic hypotheses include intravascular sequestration of toxin to a newly formed intravascular lipid phase (sink) [8, 9] and potential for enhanced initial redistribution [9]. Pharmacodynamic actions such as a substrate-induced

metabolic effect [10], ion channel modulating action [11], and direct cardiotoxicity [12] have also been posited. The relative contribution of these effects on recovery in LAST nevertheless remains unknown.

Recognizing that some of these mechanisms are not particular to local anesthetics, prior investigators have suggested that ILE might also be beneficial for intoxications with xenobiotics that share some pharmacologic homology with local anesthetics. Subsequent preclinical experiments exploring the effect of ILE in lipophilic drug toxicity from a variety of non-local anesthetic agents have on balance suggested benefit [13–17].

Clinical use of ILE in non-local anesthetic poisoning has similarly been associated with successful resuscitation outcome in numerous case reports of overdose with pharmacologically disparate agents [18–23]. However, given the variability of drugs taken in overdose and the range of both generic and specific antidotes utilized to treat cardiovascular toxicity in concert with administered ILE therapy in these cases, the magnitude of any benefit attributable to ILE administration remains unclear [24]. Systematic study of patients with severe overdose, and in particular those exhibiting cardiovascular collapse, is rendered difficult by both the rarity and unpredictability of presentation. We therefore determined to compile a prospective registry of human cases of ILE use with the purpose of documenting current utilization and informing future use.

The Lipid Injection for the Purpose of Antidotal Effect in lipophilic Medicine IntoxiCation (LIPAEMIC) study group was formed in 2009 for the purpose of undertaking the LIPID REGISTRY project—a prospective registry of human cases of ILE use. Promotion of the registry was undertaken at national and international forums, via literature publication, through linkage with the established educational website Lipid Rescue (www.lipidrescue.org), and through direct email approaches to investigators/authors of publications pertaining to use of ILE. Collection of data continued until August 2012 when the registry was closed to submissions.

This report describes the 3 years of case data collected from the LIPID REGISTRY project. Specifically, we report the 48 cases of ILE use entered onto this forum and utilize the data obtained to inform future ILE research and clinical utilization.

Methods

The LIPID REGISTRY was established in August of 2009 following collaboration between investigators of the newly created LIPAEMIC study group. Ethical approval for the project was granted from the Multicenter Ethics Committee of the New Zealand Health and Disability ethics committee. A website was constructed to support recruitment of centers as

contributors to the database. To ensure anonymity, no data which might identify individual patients was recorded.

Once registered, contributor sites were sent a unique identifier and the web address of the data collection template. All subsequent cases from a single institution were therefore identifiable. A request was made for all instances of ILE's use as an antidote from the contributing institution to be entered. The reporting template extracted demographic data, the agent and nature of ingestion, and data on all clinical outcomes. Details of concurrent therapies, and of measured clinical hemodynamic and neurologic outcomes, were specifically sought. A full copy of the data collection template is provided in Appendix 1. Retrospective reporting of cases was permitted only at the initial registration. Contributors were furthermore invited to receive interim reports of the registry dataset. Since inception, six updates have been sent to contributors, with the last being in June 2011. Decay occurred in reporting frequency to the registry over the 3 years of the project. As such, it was decided to cease active recruitment through the website in August 2012, which has been subsequently been removed.

Statistical examination of all variables was undertaken with GraphPad Prism (version 5.0, GraphPad Software Inc, La Jolla, USA. <http://www.graphpad.com/>). Descriptive statistics were used to report outcome data. The Mann–Whitney statistic and a Friedman nonparametric repeat measures analysis of variance (RMANOVA) were used as appropriate. The null hypothesis in the RMANOVA is that level of consciousness and systolic blood pressure were stable over time. Statistically significant results demonstrate an increase of parameters over time; they do not establish that ILE caused this increase. The case that ILE may have been causal in any improvement would be strengthened by a stronger temporal association: as such analysis of the time-points “pre ILE,” immediately post-ILE, and 30 min post-ILE are reported primarily. A p value of <0.05 was deemed to be statistically significant.

Results

Reporting

Sixty-one reporting sites were recruited to the registry (29 emergency departments, 24 anesthetic departments, 7 intensive care units, 1 pediatric department). Emergency departments were located in Australia (9), USA (8), New Zealand (4), UK (3), Canada (2), Iran (1), China (1), and Turkey (1). Anesthetic departments were located in UK (8), USA (6), Australia (3), France (2), New Zealand (1), Spain (1), Finland (1), Colombia (1), and Czech Republic (1). Intensive care departments were located in Australia (3),

New Zealand (1), Canada (1), Austria (1), and UK (1). The single pediatric department was in Mexico.

Forty-eight cases of ILE use as antidote were reported to the registry between August of 2009 and August of 2012 inclusive, with reports submitted by 16 of the 61 registered sites. The greatest reporting was undertaken in the first year of operation (Fig. 1). Thirty-six of these cases were collected either as a sequential collection of all uses in a center prior to enrolment or after enrolment. Twelve cases reported to the registry were for treatment prior to the date of center enrolment, the earliest being in June 2008. All of these occurred in the first year. The decrease in numbers reported over sequential years of operation suggests that capture of all cases from enrolled centers was not complete. The majority of sites reported only a single case. Numbers of reported cases from single institutions were 29 cases (1 institution), 3 cases (2 institution), 2 cases (3 institutions), and 1 case (11 institutions).

Local Anaesthetic Toxicity

Ten cases were reported of ILE use for signs of local anesthetic toxicity. Patient characteristics and details of performed nerve blocks are presented in Table 1. Ultrasound was employed to guide nerve blockade in one patient only (femoral nerve block, case 3). Four of ten patients received adjunctive adrenaline administration in conjunction with local anesthesia.

Lipid emulsion was identified as having been administered in accordance with the guideline published by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) lipid infusion guideline in five patients, and not according to any known guideline in five patients. Details of ILE administration are presented in Table 2.

Of seven patients exhibiting seizures, two received additional anticonvulsant treatment (midazolam in both; case nos. 2 and 4). In addition to ILE, the only patient suffering cardiac

arrest (pulseless electrical activity; case no. 4) also received adrenaline, sodium bicarbonate, magnesium, and hydrocortisone during resuscitation. In the opinion of the reporting physician, ILE was thought to have prevented death in three of the ten cases of local anesthetic toxicity (nos. 2, 5, and 8). No patient suffering local anesthetic-induced toxicity received hemofiltration, hemodialysis, or cardiopulmonary bypass.

Non-local Anaesthetic Toxicity

Thirty-eight cases were reported of ILE use for non-local anesthetic toxicity. The majority of ingestions were of multiple agents (Table 3). Individual patient characteristics and details of ingestants for non-local anaesthetic drug poisoning are presented in Tables 4 and 5.

Details of ILE administration after intoxication by agents other than local anesthetics are outlined in Table 6. When administered for the indication of decreased level of consciousness, six (6/30) patients received an initial bolus of ILE, four (4/30) of these subsequently received an infusion of ILE. Two (2/30) received a bolus only, and 24 (24/30) received an infusion only. When administered for the indication of cardiovascular collapse or cardiac arrest, seven (7/8) patients received an initial bolus of ILE with two (2/8) receiving a second bolus. Five patients (5/8) received an infusion of ILE following initial bolus administration for the indication of cardiovascular collapse/cardiac arrest, and one (1/8) patient received an infusion only without preceding bolus. Lipid emulsion was identified as being administered in accordance with established guidelines in local practice (24), lipidrescue.org online guideline (6), AAGBI guideline (2), American College of Medical Toxicology guideline (ACMT) (1), and no known guideline (6).

Additional pharmacologic treatments administered in patients suffering decreased LOC included flumazenil in two, glucagon in one, and naloxone in one. Additional treatments administered in patients suffering cardiovascular collapse or cardiac arrest were calcium gluconate/chloride in four, adrenaline in three, noradrenaline in three, glucagon in two, dopamine in two, charcoal in two, vasopressin in one, and *N*-acetylcysteine in one. No patient suffering non-local anesthetic-induced toxicity received hemofiltration or hemodialysis. One of the patients who subsequently died was placed on cardiopulmonary bypass on day 2 of their admission.

Analysis: ILE in Decreased Level of Consciousness

In 30 cases, ILE was used to treat obtundation attributed to intoxication by drugs other than local anesthetics. ILE was deemed by the treating physician to have contributed to the patient's recovery in 26 (26/30) patients receiving ILE for the indication of decreased level of consciousness (LOC). In four

Fig. 1 Case reports per year of operation. Cases collated at August for the preceding 12 months. Solid gray panels=sequential collection or reported after registration; speckled panel=retrospectively reported cases

Table 1 Patient characteristics, performed blocks, toxicity, and outcome

No.	Age (year)	Gender	Weight (kg)	Block	Agent	Toxicity	Survived
1	NR	M	NR	Penile	Lidocaine 2 % 28 ml	Hypertension	Yes
2	67	F	49	Axillary	Lidocaine 2 % 10 ml	Drowsy	Yes
3	NR	NR	NR	Infraclavicular rescue for failed supraclavicular	Bupivacaine 0.375 % 20 ml	Seizure	Yes
4	68	M	75	Infraclavicular	Mepivacaine 1.5 % 40 ml / mepivacaine 1.5 % 20 ml+Bupivacaine 0.5 % 20 ml	Decreased LOC	Yes
5	69	F	80	Femoral “3 in 1”	Ropivacaine 1 % 20 ml	Seizure	Yes
6	NR	NR	NR	Posterior approach Sciatic	Bupivacaine 0.5 % 30 ml	Cardiac arrest	Yes
7	NR	NR	NR	Posterior approach Sciatic	Bupivacaine 0.5 % 10 ml	Seizure	Yes
8	30	M	81	Posterior approach Sciatic	Bupivacaine 0.5 % 20 ml	Seizure	Yes
9	47	F	60	Subcutaneous	Bupivacaine 2.5 mg/ml 75 ml	Seizure	Yes
10	75	F	57	Paravertebral with catheter infusion	Bupivacaine 0.25 % 638 ml	Decreased LOC	Yes
						Seizure	Yes

NR not reported

(4/30) patients, the benefit of ILE administered for decreased LOC was considered uncertain.

Plots of Glasgow Coma Score (GCS) vs. time for patients with decreased LOC are shown in Fig. 2. The “Pre ILE” time point represents the baseline GCS prior to ILE administration. The “Post ILE” time point is that immediately post-lipid administration. Thirty minutes is 30 min post-ILE administration, “4 hr” is 4 h post-ILE administration. Lines connect the values over time for each patient.

Ten of the 38 reported patients in whom ILE was used for neurologic compromise required tracheal intubation and mechanical ventilation. In three of these, the stated indication was to gain situational control for further management rather than protection of the airway. All patients’ GCS after intubation was assumed to be 3 at subsequent time points for the purposes of statistical analysis. The increase of GCS over time from pre-ILE, post-ILE, and

30 min post-ILE was statistically significant ($p<0.0001$, Friedman nonparametric RMANOVA). The median GCS increased from 4/15 to 8/15 for the whole patient group; the median increase in GCS in individual patients over this time was 2 points. Statistical significance held when the 4 h post-time point was included in the RMANOVA ($p<0.0001$).

It has been suggested that early ILE use could paradoxically worsen intoxication from an orally ingested intoxicant, with increased blood carrying capacity serving to increase absorption of lipophilic toxin from the gastrointestinal tract [25, 26]. In order to explore this hypothesis, change in GCS between the pre-lipid (pre-ILE) time point and 30 min post (30 min) lipid was plotted against interval between ingestion and commencement of ILE. This is presented graphically in Fig. 3. No relationship between time post-ingestion and change in GCS was found ($p=0.41$, Spearman nonparametric $r=-0.15$).

Table 2 ILE administration in LA toxicity

No.	ILE	Percent	Infusion	Total volume (ml)
1	NR	NR	NR	NR
2	Intralipid®	20	1.5 ml/kg bolus then 400 ml over 20 min	500
3	NR	NR	NR	NR
4	Intralipid®	20	3×100 ml boluses	300
5	Intralipid®	20	1.5 ml/kg bolus then 400 ml/h	500
6	NR	NR	NR	NR
7	NR	NR	NR	NR
8	Lipofundin®	20	1.5 ml/kg bolus then 15 ml/min	640
9	Intralipid®	20	1.5 ml/kg bolus then 13 ml/min	900
10	Intralipid®	20	1.5 ml/kg bolus then 870 ml/h	587

NR not reported

Table 3 Agents ingested

Intoxicant	Number reported
Benzodiazepines	16
Tricyclic antidepressants	15
Other antidepressants	13
Anticonvulsants	5
Beta blockers	3
Calcium channel blockers	3
Other	17

Analysis: ILE in Cardiovascular Collapse

Eight cases of ILE administration were reported for the purpose of resuscitation from cardiovascular collapse/cardiac arrest attributable to intoxication by agents other than local anesthetics. ILE administration was thought by the treating physician to have contributed to the patient's recovery in three (3/8) cases of ILE's use to treat cardiovascular collapse/cardiac arrest. In three patients (3/8), ILE was considered of uncertain benefit in effecting recovery, while two (2/8) patients suffering cardiovascular collapse/cardiac arrest and ILE was not deemed of benefit by the attending physician. Three of eight patients who received ILE for cardiovascular collapse died during the course of their illness. None of these deaths occurred during the initial 4-h recording period.

The rise in systolic blood pressure (SBP) over time among patients treated with ILE following cardiovascular collapse was statistically significant for the time points pre-ILE, post-ILE, and 30 min post-lipid ($p=0.012$). Statistical significance held when the 4-h time point was included in the RMANOVA ($p=0.012$). The SBP over time following ILE administration for all patients is presented in Fig. 4.

Complications

No complications attributed to ILE administration were reported for the ten patients receiving ILE for the indication of local anesthetic toxicity. Of the 38 patients receiving ILE for the indication of poisoning from drugs other than local anesthetics, no specifically sought complications (infection/sepsis, allergy/anaphylaxis, thrombocytopenia, hematuria, acute lung injury, embolic phenomena) were reported. One patient exhibited mild elevation in serum amylase in the absence of clinical features of pancreatitis. This patient received ILE after intoxication with 280 mg olanzapine and an unknown amount of ethanol and lithium. Five hundred milliliters of 20 % intralipid® was administered over 30 min, followed by another 500 ml over 30 min 4 h later. A second patient had lipaemia interfere with laboratory testing of biochemical parameters for 1 h immediately after injection. This patient received ILE for

an overdose of 600–900 mg of propranolol and an unknown amount of methocarbamol. Six and one half milliliter per kilogram of 20 % intralipid® was administered over 1 h, followed by 1.6 ml/g to a total volume of 1,000 ml. One patient exhibited bronchospasm requiring intravenous salbutamol and steroids. Subsequent tryptase was negative. Three 1.5 ml/kg boluses of 20 % intralipid® was given after toxicity in a regional block with 20 ml of 1 % ropivacaine in this patient.

Discussion

Intravenous lipid emulsion was first reported to have antidotal effect in animal models in the late 1990s. Since then, use in local anesthetic systemic toxicity, and more recently use in toxidromes from drugs other than local anesthetics, has been increasingly reported [18–23]. Systematic reporting of outcomes following ILE infusion for such indications has been lacking with only single case reports, and short case series [27] appearing in literature to date. In the present work, we report the first 48 cases of ILE use in poisoning from both LAST, and drugs other than local anesthetics, from the LIPID REGISTRY project. This represents the largest systematically collated series of ILE use in current literature, with a data collection format that has enabled statistical analysis.

Thirty of 48 of cases reported pertain to the use of ILE for altered conscious state in general toxicology. These data provide an important insight into a potential effect of ILE in drug-induced obtundation, with the median GCS increasing from 4/15 prior to ILE to 8/15 30 min after ILE. The median individual increase per patient in GCS was 2 points. This effect is consistent with animal models demonstrating decreased brain drug levels when ILE is administered after initial drug distribution [28, 29]. While promising, these observations do not hold direct clinical utility. The GCS is not validated as a measure of outcome in toxicology and requires clinical contextualization in terms of the intoxicant to further inform management [30]. While association between GCS increase and time is strong, this suggests rather than establishes that ILE was causal in this increase. A median rise of 2 points in the GCS score may furthermore be statistically, but not clinically, significant. Indeed, the clinical utility of this reported increase in the present work is undetermined. These limitations notwithstanding the reporting pattern to the registry indicates an appropriately powered randomized clinical study is feasible for the use of ILE in drug-induced obtundation, and the present work provides impetus for systemic evaluation of this to be undertaken. Such studies could be powered to clinically more robust endpoints such as rates of intubation. Until trials of this nature are undertaken, we suggest that ILE use for this indication be considered experimental.

Table 4 Patient characteristics and details of ingestants for non-local anaesthetic drug poisoning, use in obtundation

No.	Age (years)	Gender	Weight (kg)	Intoxicants	Toxicity	Hrs post	GCS pre	GCS 30	Survival
1	26	F	65	Ephedrine 30 mg; caffeine 200 mg; aspirin 75 mg; alcohol NK	Altered LOC	3	13	15	Yes
2	30	M	75	Olanzapine 1,400 mg; zopiclone 315 mg; procyclidine 380 mg	Decreased LOC	3	3	4	Yes
3	61	M	80	Quetiapine 4.3 g; sertraline 3.1 g	Decreased LOC	3	3	5	Yes
4	23	M	75	Temazepam 280 mg; zopiclone 105 mg; dosulepin 1,650 mg; fluoxetine 240 mg	Decreased LOC	11	7	10	Yes
5	29	M	130	Dosulepin 900 mg; alcohol 36 u	Decreased LOC	3	7	11	Yes
6	49	F	65	Amitriptyline 420 mg; pethidine 300 mg; diazepam 26 mg	Decreased LOC	4	3	9	Yes
7	25	F	65	Quetiapine 8.7 g; alcohol 5 u	Decreased LOC	6	6	8	Yes
8	25	F	50	Quetiapine 7 g; sertraline 700 mg; clonazepam 60 mg; zopiclone 37.5 mg	Decreased LOC	5	3	8	Yes
9	53	F	75	Trazodone 2.8 g; risperidone 40 mg; lamotrigine 700 mg; clonazepam 10 mg	Decreased LOC	1.5	3	T	Yes
10	58	F	55	Olanzapine 280 mg; alcohol NK	Decreased LOC	9	6	6	Yes
11	54	F	55	Diazepam 140 mg	Decreased LOC	6	6	10	Yes
12	37	F	70	Diphenhydramine 1 g; citalopram 200 mg; alcohol NK	Decreased LOC	2	6	8	Yes
13	52	F	70	Doselepin 3 g	Decreased LOC; ECG abnormality	3	6	11	Yes
14	34	M	85	Diazepam 140 mg; sertraline 1.4 g; alcohol 15 u	Decreased LOC	1.5	3	7	Yes
15	48	F	85	Tolterodine 28 mg; lansoprazole 105 mg; quetiapine 4.2 g; gabapentin 16 g; mirtazepine 420 g; nitrazepam 70 mg	Decreased LOC	2	11	T	Yes
16	43	M	80	Amitriptyline 1,050 mg; alcohol 15 u	Decreased LOC	2	3	7	Yes
17	22	M	75	Diazepam 150 mg; alcohol 6 u	Decreased LOC	2	3	9	Yes
18	42	F	115	Procyclidine 35 mg; amisulpride 4 g; valproate 3 g; venlafaxine 1 g; diazepam 35 mg	Decreased LOC	5	7	11	Yes
19	45	F	60	Quetiapine 4.8 g; alcohol 18 u	Decreased LOC	2	3	5	Yes
20	53	F	65	Clozapine 300 mg; propranolol 140 mg	Decreased LOC	2	6	8	Yes
21	60	F	85	Amitriptyline 2.4 g	Decreased LOC; ECG abnormality	3	6	9	Yes
22	53	F	90	Olanzapine NK; dothiapipe NK; alcohol 40 u	Decreased LOC	4	3	T	Yes
23	29	F	110	Fluoxetine 280 mg; tramadol 5.6 g; clonazepam 70 mg; zopiclone 52.5 mg; pregabalin 700 mg; tolteradine 14 mg	Decreased LOC	2	3	T	Yes
24	29	F	110	Pregabalin 1,250 mg; fluoxetine 500 mg; quetiapine 4.2 g; tolterodine 14 mg; tramadol 3 g; clonazepam 21 mg; zopiclone 78.5 mg	Decreased LOC	5	3	T	Yes
25	33	F	60	Amitriptyline 1,750 mg; diazepam 42 mg; citalopram 1.4 g	Decreased LOC	5	7	9	Yes
26	35	F	60	Amitriptyline 1,250 mg; diazepam 28 mg; alcohol 7 u	Decreased LOC; ECG abnormality	4	8	9	Yes
27	17	M	75	Dosulepin 1,050 mg; codeine 21 mg; doxycycline 1.4 g; paracetamol 11 g	Decreased LOC	1.5	5	T	Yes
28	42	M	75	Amitriptyline 1.5 g; diazepam 8 mg; gabapentin 15 g	Decreased LOC	4	3	T	Yes
29	58	M	85	Amitriptyline 1,440 mg; zopiclone 104 mg	Decreased LOC	2	4	7	Yes
30	25	M	75	Clonazepam 10 mg; citalopram 1,120 mg; quetiapine 8.4 g; codeine 128 mg; paracetamol 8 g	Decreased LOC	5	3	T	Yes

NR not reported, NK not known, LOC loss of consciousness, VT ventricular tachycardia, u international units, Hrs post interval between ingestion and start ILE (hours), GCS pre GCS pre ILE, GCS 30 GCS 30 min post-ILE, T trachea intubated

Lipid emulsion was administered for cardiovascular collapse and/or overt cardiac arrest in toxicity of drugs other than local anesthetics in eight patients reported to the registry. The present evidence base for use of ILE in cardiovascular toxicity is established biologic effect in animal models coupled with case reports demonstrating strong temporal association and survival from an otherwise irretrievable position [2, 18]. On

this basis, it is reasonable that lipid be used as a rescue therapy when circulatory compromise poses an immediate threat to life and all other available treatments have failed. Descriptors of this population—a median systolic blood pressure of 70 at initiation of ILE and an overall mortality of 38 %—suggest the population reported to the registry was consistent with this described indication. Improvement in systolic blood pressure

Table 5 Patient characteristics and details of ingestants for non-local anaesthetic drug poisoning, use in cardiovascular collapse

Number	Age	Gender	Weight	Intoxicant	Toxicity	Hrs post	Treatments before ILE	Survival
1	71	M	75	Verapamil SR 9,640 mg	Cardiovascular collapse	36	Calcium, sodium bicarbonate, noradrenaline	No
2	28	M	80	Amitriptyline 4.25 g	Hemodynamic instability hours after cardiac arrest	6	Adrenaline, noradrenaline, sodium bicarbonate	Yes
3	51	M	75	Amitriptyline >2 g; quetiapine NK; citalopram NK; quinapril NK	Cardiovascular collapse; ECG abnormality	1.5	Charcoal, sodium bicarbonate	Yes
4	39	F	70	Metoprolol NK; accupril NK; furosemide NK; amlodipine NK	Cardiovascular collapse; ECG abnormality	4	Noradrenaline, adrenaline, calcium, glucagon	No
5	NR	NR	NR	Dothiepin 450 mg; amlodipine 20 mg	Cardiovascular collapse; VT	2	Charcoal, sodium bicarbonate, calcium	Yes
6	33	F	61	Propafenone NK	Cardiovascular collapse; cardiac arrest	4	Adrenaline, dopamine, sodium bicarbonate, calcium	Yes
7	25	F	76	Propranolol 600–900 mg; methocarbamol NK	Cardiovascular collapse	5	Noradrenaline, adrenaline, glucagon	Yes
8	49	M	93	Quetiapine >2 g	Cardiovascular collapse; wide complex tachycardia	2	Noradrenaline, adrenaline	No

NR not reported, NK not known, LOC loss of consciousness, VT ventricular tachycardia, u international units, Hrs post interval between ingestion and start ILE (hour)

was seen over time after ILE administration, with an increase in median SBP from 70 to 90 from pre-ILE to 30 min post-ILE. Three of eight treating clinicians attributed recovery to lipid infusion. In one case, there was a cessation in the need for vasoactive amines. Given the nature of reporting, the number of concurrent treatments, and the absence of any control group, it is clearly impossible to ascribe causation in recovery to administered ILE. The pattern of blood pressure improvement is, however, consistent with what is seen experimentally and in clinical reports of decreased free drug levels commensurate with the use of ILE [8–11, 31].

The presented dataset contains fewer cases of ILE use for manifestations of LAST, with predominantly CNS manifestations (seizure, altered level of consciousness) reported. Bupivacaine was the most commonly reported offending local anesthetic again in keeping with the known relative frequency of its use and toxicity. All ten cases of LAST exhibited a positive outcome following ILE administration. ILE use was nevertheless attributed as causal in patient recovery in only three of these, and only one where the patient experienced cardiovascular collapse.

Reporting on adverse effects for lipid was based on specific survey questions asking for presence of infection/sepsis, allergy/anaphylaxis, thrombocytopenia, hematuria, acute lung injury, or embolic phenomena and a general question asking if any other adverse effects were thought by the respondent to be secondary to ILE. Adverse effects reported for lipid were limited to three cases: one serious event where immediate clinical effects were noted consistent with a possible bronchospastic reaction, one case of hyperamylasemia, and one case of interference with laboratory analysis—a recognized adverse effect of ILE. The infrequency of serious adverse events in this study is reassuring and parallels the observations in case series, case reports, and systematic reviews where serious reactions have not been noted [32]. However, caution should be exercised in estimates of safety based on low overall numbers. Serious adverse events with any drug therapy may be rare and require many thousands of administrations to identify an effect which holds clinical significance. The risk–benefit ratio presently appears quite low in severe cardiovascular toxicity. Use of ILE in the treatment of intoxications with low potential for lethality, such as

Table 6 ILE in non-local anaesthetic toxicity

Indication	Bolus (ml/kg)	Infusion (ml/h)	Total vol (ml)	Formulation
Decreased LOC (N=30)	3.1 (1.2) N=6	372 (70) N=30	531 (22) N=30	Intralipid 20 % N=30
Cardiovascular collapse/ Cardiac arrest (N=8)	2.1 (0.7) N=7	482 (237) N=6	587 (129) N=8	Intralipid 20 % N=8

All data mean (SD)

Fig. 2 Plot of GCS vs. time: general toxicology patients ($n=30$)

isolated decreased GCS, should remain tempered with caution. The predominance of altered conscious state as the indication for use of ILE within these data may mean the low frequency of adverse events seen does not generalize to all uses in toxicology. The adverse effect profile for ILE could conceivably be different for a group of patients where the indication for use is a critically compromised circulation. It is also possible that laboratory interference and pancreatic complications may have been underreported as they did not appear in the specific complications sought in the survey.

Concern has recently been raised that increasing blood carriage capacity for toxin in the absorptive phase of intoxication with early administration of ILE might increase absorption from the GI tract, paradoxically increasing intoxication [25, 26]. The improvements seen over time in level of consciousness and blood pressure suggest this was not a major effect in the cases reported to the registry. Post hoc analyses were undertaken with the level of consciousness data seeking any relationship between in change in GCS over time from initiation of ILE to 30 min after infusion and time post-ingestion ILE was initiated. The expected relationship if ILE caused increased absorption is that less clinical improvement should occur if ILE is used earlier after ingestion. While not precluding the possibility of such a relationship, this effect

Fig. 3 Change in GCS (delta GCS) vs. interval between ingestion and start ILE ($p=0.41$, Spearman nonparametric $r=-0.15$)

Fig. 4 Plot of SBP vs. time: general toxicology patients, cardiovascular collapse indication

was not seen in the dataset. Further laboratory and clinical study of this phenomenon are warranted.

Guidelines outlining administration of ILE have been written by a number of authorities over the last decade [6, 7]. Accordingly, when administered in LAST or in cardiovascular collapse secondary to a non-local anesthetic drug, the majority of respondents indicated administration of a bolus then subsequent infusion in line with such a guideline (AAGBI, lipidrescue®, ACMT). In the setting of obtundation, the great majority of reported uses were from a single center. As clinical urgency was lessened for this indication relative to cardiovascular collapse, an “infusion only” (i.e., without bolus) was commonly used.

The present work is subject to a number of limitations. Case report data provide a significant part in the justification for use of ILE in toxicology. Such data nevertheless suffer inherently from various biases limiting generalization. Publication bias potentially favors dissemination of positive outcomes associated with any novel therapy. In the literature on ILE, reports of successful outcome significantly outweigh those of treatment failure. One of the desired functions of the LIPID REGISTRY project was to mitigate any publication barrier based on outcome. While the potential for reporting bias remains, the mortality in use for cardiovascular collapse and the rate of endotracheal intubation in the general toxicology patients suggests this goal was met at least in part. Initial inclusion of retrospective cases, and potential for incomplete capture of all consecutive cases of ILE use at reporting sites, may additionally have contributed to the observed decline in numbers of cases reported over the 3-year period of the registry.

In the absence of any control group, what is proven by returned statistical significance is that reported parameters improved over time. This allows support for the view that ILE is associated with improvement, without establishing this as a causal relationship. This support is somewhat strengthened by a short timeframe of testing: temporal association strengthens the likelihood of a causal relation. The use of RMANOVA is statistically conservative, each patient in part acting as their own control for changes over time.

There are a number of potential biases within this dataset. There is significant single center bias, which could limit external validity. As the majority of reported uses were for

the non-standard indication of altered conscious state rather than the more accepted indication of shock unresponsive to other measures. The lesser acuity for those with altered conscious state will tend to bias endpoints such as death in favor of ILE in the overall registry population. These data are unblinded, with the inherent potential to bias results. While systematically collected, recordings such as GCS do have some subjective component. Though these factors mitigate the strength of conclusions that can be drawn, the less formal nature of the registry enabled cases to be reported which might otherwise have been lost to systematic enquiry. Such an approach may prove of merit in the investigation of other agents awaiting randomized clinical trial evidence, such as therapeutic euglycemic hyperinsulinemia [33, 34].

Some cases entered into the registry have additionally been previously reported on elsewhere in the literature. The decision was made to include such cases as reporting occurred using the registry template, which contributed to a new pooled analysis. The dataset is also skewed somewhat toward one center's experience, with 30 of the reported cases coming from one unit. While this has the potential for biasing reports, these cases were collected sequentially over a short period. A volume of data on sequential uses such as this is rare in the literature on ILE.

Despite significant methodologic limitations inherent in conduction of a study such as this we have nevertheless compiled a volume of data on sequential uses of ILE that remains unique within toxicology literature on the subject. Given the limitations of such a dataset, significant caution must be applied in recommendation for ILE use on the basis of the findings herein. Rather, these results may be most gainfully employed to encourage and power systematic clinical study on the various applications for ILE in clinical toxicology.

Conclusions

Improvements in GCS for patients with drug-induced central nervous system toxicity, and in systolic blood pressure for shocked overdose patients, were observed following injection of lipid emulsion in this series of patients reported to the lipid registry. Few adverse effects were recorded, albeit some proved clinically significant. Clinical trials and the reporting of drug concentrations after ILE use are warranted to further define the role of ILE in clinical toxicology.

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