The Occasional intralipid emulsion therapy

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INTRODUCTION

Intravenous lipid emulsions (ILEs) are fats that can be delivered parenterally as boluses or as infusions. ILE provides dietary fats in total parenteral nutrition (TPN), but it has also been studied and used in the treatment of drug overdoses. ILE is a first-line treatment for local anaesthetic systemic toxicity (LAST), a serious complication of regional nerve block.[1,2] Some literature also suggests that ILE may be effective as rescue therapy for lipophilic drug overdoses, including tricyclic antidepressants (TCAs), beta-blockers, calcium-channel blockers (CCBs), bupropion and venlafaxine.[2,3]

The exact mechanism of ILE therapy in the treatment of acute lipophilic drug toxicity remains unclear despite decades of publications. ILE may act as a 'lipid sink' by trapping lipophilic drug molecules and rendering them biologically inactive.[4] Other theories include ILE helping shuttle encapsulated lipophilic toxins to the liver and/or kidney for elimination[5,6] and improving cardiac function by providing the myocardium with readily available fatty acids for energy.[4,7] Finally, ILE may mitigate hypotension during overdose by decreasing nitric oxide-induced vasodilation.[8]

ILE is a shelf-stable drug. Settings where doctors administer local anaesthetics should stock ILE and establish treatment protocols to be able to use ILE for LAST. Emergency departments could potentially improve patient outcomes in life-threatening lipophilic drug overdoses if ILE was stocked and staff trained in using ILE as rescue therapy.

INTRAVENOUS LIPID EMULSION AS FIRST-LINE TREATMENT FOR LOCAL ANESTHETIC SYSTEMIC TOXICITY

LAST is a rare but life-threatening complication of a local anaesthetic administration. Patients are at higher risk for developing LAST if local anaesthetic is administered at a highly vascular site, such as intercostal nerve blocks and epidural anaesthesia.[1] The presentation of LAST is variable and should be suspected with unexpected physiological changes that occur after administering local anaesthetic.

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Symptoms of LAST include initial central nervous system (CNS) excitement (perioral numbness, metallic taste, mental status changes, anxiety, visual changes, muscle twitching and seizures), CNS depression (somnolence, coma and respiratory depression) and cardiovascular changes (tachycardia, bradycardia, hypertension, hypotension, ventricular arrhythmias and asystole).[9,10]

Consult a medical toxicologist or Poison Control Centre for assistance when LAST is suspected. As bupivacaine is the most commonly used drug for nerve blocks, ILE should be administered immediately and simultaneously with advanced cardiac life support with bupivacaine-induced LAST.[1,2] ILE should also be considered treatment for LAST due to other local anaesthetics.

INTRAVENOUS LIPID EMULSION AS RESCUE TREATMENT

Since 2006, case series and case reports describe using ILE as rescue therapy in certain life-threatening lipophilic drug toxicities other than LAST.[11-17] There have been no controlled human trials evaluating the efficacy or potential adverse effects of ILE as rescue therapy in treating TCA, beta-blocker (BB) or CCB toxicity.[3] Randomised control animal studies and various human case studies offer very low-quality evidence with heterogeneous results.[3] Higher quality dose-finding and controlled human clinical studies are required to advance the knowledge of ILE as a rescue therapy for drug overdose, including establishing a number needed to treat and a number needed to harm. The current clinical recommendations to inform the use of ILE as rescue therapy for non-LA(Non-local anesthetic) drug overdoses were established by an expert consensus group, the lipid emulsion workgroup, and were informed by systematic reviews including animal studies and human case studies.[2] To ensure that the treatment of lipophilic toxic drug overdoses is treated with the most up-to-date evidence, medical toxicologists or a Poison Control Centre should be routinely consulted for their expert guidance. Smolinske *et al*.[18] highlight that, in the USA alone, the 'published cases of failed lipid emulsion therapy outnumber the published instances of ILE success', and caution that ILE therapy in non-local anaesthetic overdose requires further study.

TRICYCLIC ANTIDEPRESSANT OVERDOSE

ILE can be used in life-threatening amitriptyline or other TCA toxicity that is refractory to first-line treatment.[2] In non-life-threatening amitriptyline or other TCA overdoses, ILE should not be used.[2] Life-threatening TCA toxicity presents with mental status changes (sedation, delirium and confusion), hallucinations, seizures, cardiac dysrhythmias (sinus tachycardia and QRS interval prolongation >100 ms), hypotension and anticholinergic toxicity (flushing, hyperthermia, dilated pupils and urinary retention).[19-21] Mortality from TCA overdose is most often associated with refractory hypotension.[19] First-line treatment for life-threatening amitriptyline or other TCA overdose is to stabilize circulation, airway and breathing:

- Administer 1 g/kg orally activated charcoal if the patient presents the timeframe for decontamination recommended by your Poison Control Centre of a potentially toxic TCA ingestion, after considering the risk of airway compromise or aspiration versus the benefit expected from gastrointestinal decontamination[22]
- Administer IV bolus crystalloid for hypotension (500–1000 mL)[23]
- If the QRS >100 ms (2.5 small boxes on a regular electrocardiogram), challenge with IV sodium bicarbonate (1–2 mmol/kg up to 150 mmol/kg [an ampule of sodium bicarbonate has 50 mmol in 50 mL]) and assess for QRS narrowing.[24] Consult a Poison Control Centre or toxicologist to determine if a sodium bicarbonate infusion is indicated for your patient[25] but do not delay if the QRS is wide
- Administer a vasopressor (norepinephrine) if volume resuscitation or bicarbonate fails to improve hypotension.[23]

If the patient fails to respond to first-line treatment, administer ILE.[2]

BETA-BLOCKER AND CALCIUM-CHANNEL BLOCKER OVERDOSE

ILE can be used as a rescue therapy in life-threatening BB or CCB overdoses that are

refractory to first-line treatment, particularly in cases presenting with cardiac arrest.[2] Differentiating between dihydropyridine and non-dihydropyridine CCBs in overdose is not particularly useful as CCBs lose their selectivity for myocytes and smooth muscle cell in overdose.[26] In an observational study of fatal poisoning cases, in which ILE was used, more than 50% of the cases included involved either a CCB or a BB.[18] In non-life-threatening BB and CCB toxicity, ILE should not be used.[2] Life-threatening BB and CCB toxicity will commonly present with bradycardia and hypotension; myocardial depression and cardiac shock may also occur.[27,28] Ventricular dysrhythmias, mental status change, hyperglycaemia (CCB), hypoglycaemia (BB) and bronchospasm are other potential effects of severe BB and CCB toxicity.[27,28] Standard treatment for acute life-threatening BB and CCB toxicity is to stabilise circulation, airway and breathing:

- If a patient presents with a potentially toxic ingestion within the timeframe for decontamination recommended by your Poison Control Centre, administer 1 g/kg[22] after considering the risk of airway compromise or aspiration versus the benefit expected from gastrointestinal decontamination
- Administer IV bolus crystalloid for hypotension (500–1000 mL isotonic saline)[29]
- Administer a vasopressor, IV high-dose insulin and dextrose if no response to 1000 mL fluid bolus[29]
- Note that atropine is often ineffective in large CCB overdose cases and clinicians should move onto other treatments quickly.[25]

For scenarios that are refractory to standard treatment, the following treatments should be administered in succession. Consult with a medical toxicologist or the Poison Control Centre for management support.

- IV calcium (CCB)
- IV ILE
- Whole bowel irrigation (for modified-release preparations).

BUPROPION OVERDOSE

Bupropion's primary toxic effects are seizure, tachycardia and agitation. With large ingestions, status epilepticus, haemodynamic collapse, cardiac arrest and death are possible. Bupropion has a narrow therapeutic window that lowers the seizure threshold even at therapeutic doses.[30] The lowest dose which has been associated with seizure is 575 mg.[31] With overdoses over approximately 3 g, seizures become increasingly likely.[31] Early consultation with a Poison Control Centre or toxicologist is recommended.

Preliminary treatment of a bupropion toxic ingestion:

- Administer 1 g/kg orally of activated charcoal if the patient presents within the timeframe for decontamination recommended by your Poison Control Centre and after considering the risk of airway compromise or aspiration versus the benefit expected from gastrointestinal decontamination[22]
- Administer IV bolus crystalloid for hypotension (500–1000 mL isotonic saline)
- Treat seizures with IV benzodiazepines and/or phenobarbital[32]
- If hypotensive, administer a vasopressor.

For scenarios that are refractory to standard treatment, the following treatments should be administered in succession. Consult with a medical toxicologist or the Poison Control Centre for management support. Bupropion can widen the QRS complex, but this is caused by reduced cardiac intercellular coupling, rather than cardiac sodium channel blockade; thus sodium bicarbonate treatment can be tried but may not be helpful.[33] ILE can be used off-label when recommended by a toxicologist for haemodynamic collapse. Extracorporeal membrane oxygenation has also been used successfully in limited case studies,[34] but this is difficult to access promptly in the rural setting.

VENLAFAXINE OVERDOSE

Venlafaxine overdose can cause life-threatening seizures, cardiotoxicity, serotonin syndrome and hypoglycaemia. Venlafaxine is not only a serotonin and noradrenaline reuptake inhibitor but also exhibits rate-dependent sodium channel-blocking activity.[35] The noradrenergic reuptake inhibition may lead to myocardial damage without severe cardiac conduction abnormalities,[36] so symptoms of left ventricular failure must be monitored in

addition to QT prolongation, which is rare.[37] Seizures can occur with venlafaxine use in the therapeutic range, but the risk increases with dose. The risk of seizure approaches 100% with a dose of more than 4.5 g.[38]

TREATMENT

- Administer 1 g/kg orally of activated charcoal if the patient presents within the timeframe for decontamination recommended by your Poison Control Centre and after considering the risk of airway compromise or aspiration versus the benefit expected from gastrointestinal decontamination[22]
- Administer IV benzodiazepines (may require high doses, if refractory, consider propofol or barbiturates)
- Cooling, intubation, ventilation and paralysis for serotonin toxicity
- Hypotension not responding to fluids may respond to vasopressors such as norepinephrine
- Recurrent episodes of hypoglycaemia can be treated with octreotide
- If QRS wide, correct electrolytes, consider administering sodium bicarbonate
- In consultation with PCC and a toxicologist, consider ILE for patients who deteriorate rapidly or who do not respond to above.

ADMINISTERING INTRAVENOUS LIPID EMULSION

Please consult the Canadian Antidote Guide in Acute Care Toxicity (https://www.ciusss-capitalenationale.gouv.qc.ca/en/antidotes) or their free app for the latest recommendations on how to administer antidotes.

Lipid emulsion therapy for lipophilic drug overdose is administered through a 20% lipid emulsion bolus, based on the patient ideal body weight:

- If ≤70 kg, administer IV bolus 1–1.5 mL/kg of 20% lipid emulsion over 1 min[39]
- In cases of cardiac arrest with no response to the first bolus dose, bolus doses can be repeated every 3–5 min for a total of 3 bolus doses[39]
- The recommended maximum total ILE dose is 8–10 mL/kg.[39]

Intralipid® 20% lipid emulsion is the most commonly used and studied ILE formulation.[2] The risk of adverse effects of ILE, especially at doses beyond 8 mL/kg, is not negligible and must be weighed against the risk of further harm resulting from the poisoning.

ADVERSE EFFECTS OF INTRAVENOUS LIPID EMULSION

The number needed to harm, the risks and the adverse effects of high-dose ILE for acute lipophilic drug toxicity remain unclear as adverse effects have not been studied at the doses suggested for ILE. Their presence or absence is not systematically reported in the ILE literature.

Adverse effects based on the extrapolation of the therapeutic administration of TPN, overdose of TPN and ILE-treated drug overdose cases include:

- Interference with laboratory measures: Serum glucose, magnesium, creatinine and lipase.[3] Centrifugation can be used to mitigate interference with certain but not all analyses
- Acute kidney injury[40]
- Cardiac arrest[40]
- Pancreatitis[40]
- Fat overload syndrome[40]
- Fat embolism[40]
- Respiratory complications ranging from simple hypoxia to acute respiratory distress syndrome[40]
- Deep-vein thrombosis[40]
- Infection
- Hypersensitivity reactions
- Extracorporeal circulation machine obstruction.[40,41]

Further clinical study is needed to understand the adverse effects in the setting of ILE for acute lipophilic drug overdose in humans. However, in the context of life-threatening toxicity failing all other therapeutic measures, the potential benefit of ILE may outweigh the potential adverse effects related to ILE therapy alone.

ORDERING INTRAVENOUS LIPID EMULSION

Intralipid® 20% is the most studied and recommended ILE formulation for drug toxicity

in the Canadian healthcare system.[2] Other ILE formulations include Nutrilipid 20% and Liposyn III, although these have not been studied for use in acute poisoning and should not be used to treat overdoses. Other ILE formulations of 10% or 30% lipid emulsion exist but should not be used in acute poisoning. We acknowledge the inherent commercial bias in this recommendation. As stewards of healthcare resources, healthcare providers must weigh the costs and benefits of ILE to justify commercial drug purchases. Smaller hospital and healthcare settings that do not stock ILE for TPN purposes may consider stocking ILE for acute drug toxicity.

Intralipid® 20% can be ordered from McKesson Canada in boxes of 6–10 100 mL, 250 mL, 500 mL or 1000 mL bags. The cost per box of bags ranges from approximately $110.00 to $200.00. It has a shelf-life stability of approximately 1 year. Smaller healthcare settings that stock ILE for acute drug toxicity should maximise its usage and cost by cycling unused and nearly expired ILE doses to tertiary centres that could use it for TPN.

To conclude, ILE is a first-line antidote treatment for LAST and can be considered rescue treatment in TCA, BB, CCB, bupropion and venlafaxine overdose.[2,3] Consult a medical toxicologist or Poison Control Centre for support in managing these drug toxicities.

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