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# “CHEWING THE FAT”

## Intravenous Lipid Emulsions

### Non nutritive uses

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## INTRAVENOUS LIPID EMULSION THERAPY

### INTRODUCTION

Sir William Courten, a 17th century English naturalist, was the first person to use an oil infusion. He administered olive oil intravenously to a dog that subsequently demised. This was attributed to a pulmonary embolus. Experimentation with oil infusions continued for decades until it was discovered that fats could only be safely administered intravenously as an emulsion. In 1962, physician and nutritionist, Professor Arvid Wretlind of Sweden (Figure 1), developed the first safe parenteral fat emulsion, which was approved for use in Europe, and over a decade later in the USA (1). This formulation is still marketed today as Intralipid®. His discovery was initiated by an interest in the nutritional support of patients at the end of World War 2. Currently, there are two types of lipid emulsions which are marketed (2):

- Pure – contains 100% soybean oil (Intralipid® and Liposyn III®) and
- Mixed – contains a 50:50 blend of soybean oil and safflower oil (Liposyn II®).

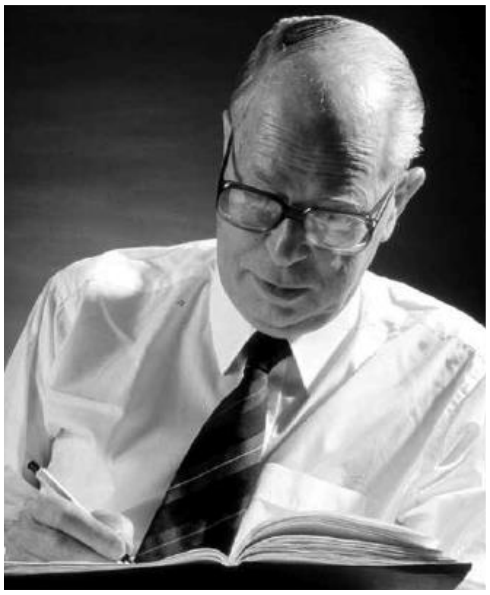

Figure 1: Arvid Wretlind 1919-2003

### CHARACTERISTICS OF LIPID EMULSIONS

As Sir William Courten demonstrated, infusing pure oil intravenously is lethal. In order to safely administer oil intravenously, the lipid source must be broken up into smaller droplets i.e. an emulsion. An emulsion is a combination of liquids that don't usually mix and the droplets of one liquid are dispersed into a second liquid (3). For clinical application not more than 0.05% of the lipid droplets in an emulsion should have a diameter greater than 5 µm as that is the diameter of the smallest blood vessels in the lung (4). Oil-in-water emulsions are commonly used and will be discussed in this booklet. However, there is ongoing research regarding formulations such as oil-in-oil and other emulsions (4).

The lipid droplets dispersed in water represent the incontinuous lipid phase, whilst the water represents the continuous aqueous phase of the emulsion(3). In order to maintain the stability of the emulsion the oil droplets must not coalesce; this is prevented by the addition of an emulsifying agent.

Intravenous lipid emulsions are complex products consisting of a cocktail of (see Figure 2):

**1. One or more triglyceride containing oils**

A range of oil sources have been successfully used over the years. Soybean and safflower oil have dominated clinical use over the last four decades. Thereafter coconut, fish, olive oil and synthetic structured triglycerides were introduced. The type of oil used determines the emulsion's fatty acid composition i.e. the ratio of medium chain triglycerides (MCT) to long chain triglycerides (LCT). This is of relevance as MCT and LCT have their own pharmacokinetic and pharmacodynamic properties.

LCT based oils such as soybean and safflower have a higher content of polyunsaturated fatty acids which can result in significant adverse effects. These include immunosuppression, enhanced proinflammatory mediator production, liver dysfunction, lipid peroxidation of omega 3, 6 and cell death.

MCT based oils such as coconut oil were mixed with soybean oil in a LCT: MCT ratio of 1:1. The purpose was to minimise the adverse effects of LCT based emulsions, by reducing the omega 6 polyunsaturated fatty acid content. When MCT were used, the aforementioned adverse effects associated with LCT were negated (2). Furthermore, MCT have the advantage of rapid plasma clearance and tissue utilization, because their use is independent of carnitine cotransport into the mitochondria for further metabolism (5). But, MCT are not without problems as ketosis formation and increased energy expenditure have been documented.

Emulsions containing a mixture of both MCT and LCT seem to be tolerated better than single triglyceride formulations.

**2. A phospholipid emulsifier**

Emulsion instability describes the physical changes (i.e. aggregation, creaming and droplet growth) which occur in an emulsion over time. A phospholipid emulsifier is an amphiphilic agent that has both hydrophilic and lipophilic ends which form a layer around the oil droplets. This acts as both a mechanical and electrical barrier to the aqueous phase. The polar hydrophilic end is directed at the aqueous phase in a dissociated form conferring an anionic charge to it. This provides a repulsive force thus preventing coalescence of lipid droplets (3). This also maintains the reduced oil droplet size which decreases the risk of emboli.

There are both natural and synthetic emulsifiers available. Egg yolk lecithin has been used extensively as it is biologically inert, non-toxic and metabolised as a natural fat in the body. A rare side effect is haemolysis, which is due to hydrolysis of the natural lecithin during the emulsification process (2).

### 3. Aqueous phase

This consists of water for injection containing additives: *tonicity modifiers, antioxidants, pH adjusters and sometimes antimicrobial agents*

- Tonicity modifiers – These impart an isotonic quality to the emulsion when introduced into the plasma. Examples are glycerine, sorbitol or xylitol.
- Antioxidants – These provide oxidative stability in the emulsion. Lipid peroxides in emulsions that are already present or formed on the shelf, can cause emulsion instability by initiating oxidation of susceptible compounds (2). Thioglycolic acid, α-tocopherol, ascorbic acid and deferoxamine mesylate are generally used to prevent oxidative instability.
- pH adjusters – the pH of the emulsion becomes acidic due to the sterilisation process and the formation of free fatty acids during storage. Small amounts of sodium hydroxide are added to adjust the pH to more alkaline.
- Antimicrobials – These are sometimes added to prevent microbial growth. For example the emulsion formulation of Propofol, Diprivan®, contains antimicrobial agents ethylenediamine tetra-acetic acid (EDTA), sodium benzoate and 9benzyl alcohol.

Intralipid® consists of 20% soybean oil, 1.2% egg yolk phospholipid as the emulsifier, 2.25% glycerine, sodium hydroxide and water.

Degradation of the emulsions may be caused by (6),(7) :

- Change in pH or addition of electrolyte containing liquids – these will negate the repellent negative charge at the oil droplet surface
- Increased temperature and freeze-thawing (Intralipid® should be stored at temperature <25°C but not frozen)
- Severe agitation

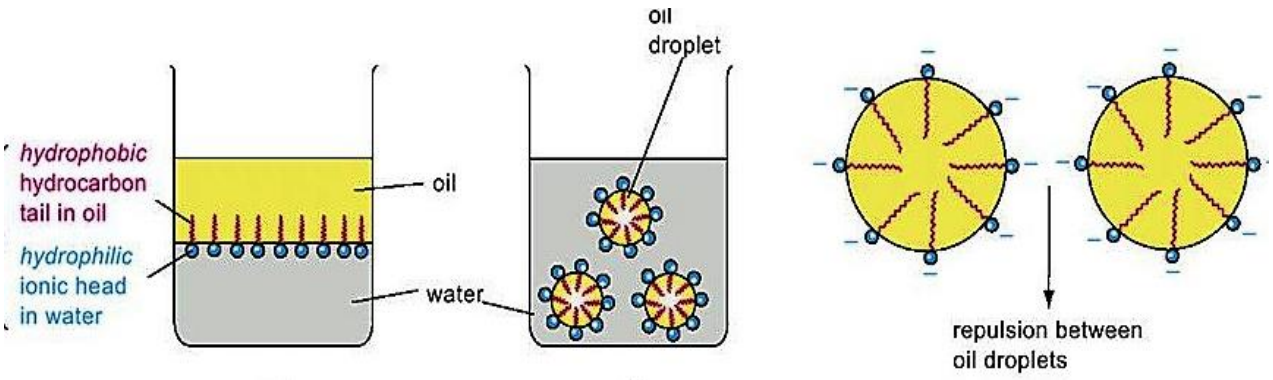


**Figure 2:** Oil droplets in an aqueous medium repel each other by a surrounding monolayer of emulsifying agent (8).

### Metabolism of intravenous fat emulsions

The metabolism of intravenous fat emulsions (IVFE) is suggested to be similar to that of chylomicrons in the body. They are cleared in two ways – metabolised as endogenous chylomicrons or by the mononuclear phagocyte system (2). Emulsion metabolism depends on the type of oil phase used as each has its' specific characteristics. MCT are extensively metabolised and rapidly cleared from the circulation, whereas LCT are poorly metabolised and are slowly eliminated from the circulation(4).

Initially the oil droplets are hydrolysed by the enzyme lipoprotein lipase, releasing triglycerides, free fatty acids, glycerin, and phospholipid (see Figure 2) (5). The triglycerides are further distributed, hydrolysed and taken up by the liver. Free fatty acids are used as an energy source or stored in adipose tissue (2). Administration of an IVFE to adults at a rate >2.5 g lipid/kg/day may result in an excessive lipid load.

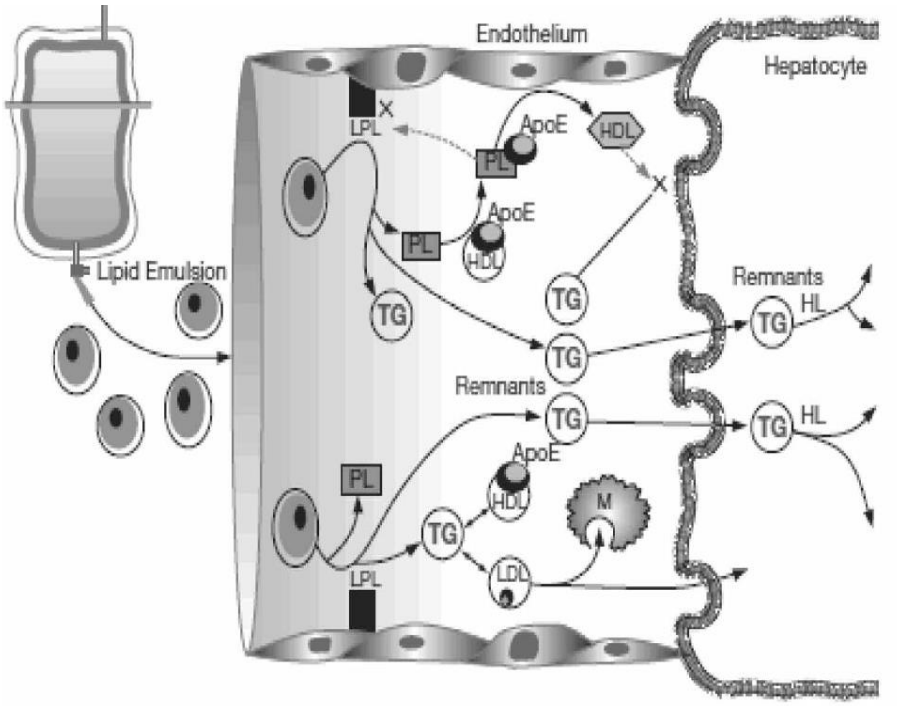


**Figure 1.** Metabolism of parenteral lipid emulsions. Lipoprotein lipase (LPL) anchored to the endothelial cell layer of venous blood vessels hydrolyzes emulsion droplets into triglycerides (TG) and phospholipids (PL). TG remnants resulting from the peripheral hydrolysis of the emulsion droplets are further hydrolyzed by the liver at endothelial sites or within hepatocytes by the enzyme hepatic lipase (HL). TG released during peripheral hydrolysis acquire apolipoproteins (Apo) to form low-density lipoproteins (LDL; Apo B-100) and/or high-density lipoproteins (HDL; Apo E). LDL particles may be taken up by hepatocytes or macrophages (M), both of which express endocytic LDL receptors. PL released during peripheral hydrolysis can interact with HDL to acquire Apo E; this complex is subsequently converted to free-cholesterol–phospholipid complexes (FC) via interaction with endothelial cell membranes. PL-Apo E complexes can decrease the enzymatic activity of LPL (arrow X), potentially diminishing peripheral hydrolysis and thereby increasing TG concentrations and the number of emulsion droplets being shunted to the liver. FC complexes can inhibit the endocytic uptake of TG remnants by the liver (arrow X), again increasing TG concentrations.

Figure 2: **Metabolism of parenteral lipid emulsions (5)**

## MANAGEMENT OF DRUG TOXICITY

1. Local anaesthetic systemic toxicity (LAST)
2. Other lipophilic drug toxicity

## LAST

The safe administration of intravenous lipid emulsions (ILE) sparked interest in its potential non-nutritive uses. In the last century ILE has formed a ground breaking addition to the management of local anaesthetic systemic toxicity. The introduction of local anaesthetic use in medicine began in the 16$^{th}$ century when coca plants were brought to Europe (9). With increasing local anaesthetic use, the frequency of cardiovascular and neurological systemic toxicity increased, prompting the development of less toxic agents.

The perfect balance between favourable effects of local anaesthetics (such as potency, rapid onset of action, and use with different routes of administration) and limited toxicity always proved difficult. All agents were shown to have the potential to cause systemic toxicity. In 1930, Tetracaine was the last ester structure of local anaesthetics to be developed; thereafter only amide type drugs were made. The first severe cardiovascular toxicity following local anaesthetic use was described by Eddie and Deutsch in 1977. Ventricular fibrillation was reported after an interscalene block was administered using 100mg of bupivacaine (9). LAST can be severe and even fatal, prompting the invention of new less toxic agents as well additive agents to limit toxicity.

### Mechanisms of intravenous lipid emulsion (ILE) therapy in the management of LAST

ILE has only recently been recommended as part of the management of LAST. How did this come to be? With the ongoing animal studies and case reports focusing on LAST, the usefulness of ILE was found unintentionally from laboratory and clinical observation. One of the cases involved a patient with carnitine deficiency suffering from LAST (ventricular arrhythmias and haemodynamic instability) shortly after administration of a local anaesthetic containing tumescent solution (9). It was theorized from this case that carnitine deficiency was a risk factor for developing LAST. It was also demonstrated that bupivacaine inhibits carnitine metabolism (by inhibiting carnitine acyl carnitine translocase) in cardiac cell mitochondria (10).

The arrhythmogenic potential of fatty acyl would go against the beneficial effects of lipid infusion in LAST. In a study done in 1998 the converse of this was observed in rats pre-treated with ILE; it caused a shift in the dose response curve where it increased the median lethal dose (LD 50) of intravenous bupivacaine (11). Animal studies in 2003 using dogs as the subjects confirmed the success of ILE use in the resuscitation and recovery from LAST. All dogs in the control group died whereas all six dogs in the experimental group showed recovery from cardiovascular collapse after the administration of ILE and internal cardiac massage.

The first clinical translation of this in human cases was described by Rosenblatt et al and Lis et al in 2006 where two patients suffered severe LAST and didn't respond to ACLS measures, but shortly after ILE therapy, there was a rapid response and recovery from haemodynamic collapse. Since then many case reports have been submitted involving the successful resuscitation from several local anaesthetics including bupivacaine, mepivacaine, ropivacaine and mepivacaine. There has also been success with the use of

different lipid emulsion formulations and it has been suggested that the type of lipid emulsion does not make a difference in the emergency situation (3). Local anaesthetics affect several cellular functions which can make their toxicity refractory to traditional resuscitation.

**Lipid Sink Theory**

This was the original theory proposed by Weinberg et al in 1998 (11). It suggests that when a lipid emulsion is infused into the blood, it forms a lipid compartment into which the lipophilic drug (local anaesthetic) can be drawn into from the aqueous medium. As the drug accumulates in the "lipid sink", a concentration gradient develops between the tissue which is highly concentrated with local anaesthetic, augmenting movement of the drug out of these tissues and into the lipid sink. This would in effect reduce tissue concentrations and binding of local anaesthetic agent and reduce toxic effects. The lipophilicity of bupivacaine and the high octanol/water partition coefficient (log P) supported the idea that lipid emulsions retain lipophilic drugs (9).

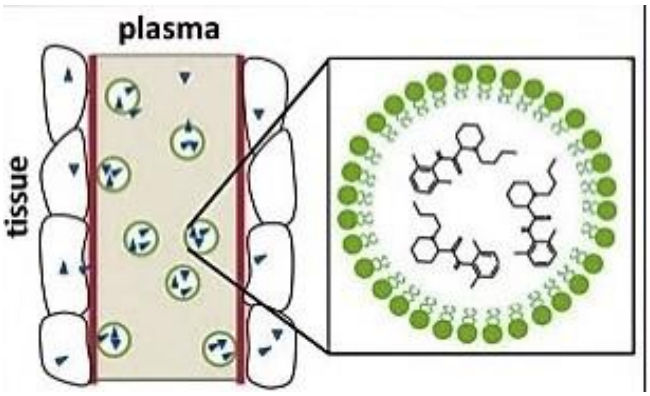


**Figure 3:** Lipid droplets trap drug molecules; reducing the free drug concentration in the plasma and consequently the drug content of the neighbouring tissue. Adapted from (12)

There is both direct and indirect evidence to support this:

**Direct Evidence**

1. Mazoit et al (13) – In vitro studies showed that lipid emulsions have a high binding capacity for and bind large amounts of lipophilic local anaesthetic. The triglyceride components of the oil emulsion used determines the affinity for lipophilic local anaesthetics. Long chain triglyceride containing emulsions bind 2-3 times more local anaesthetic than an emulsion containing a mixture of LCT and MCT. They also showed that the amount of local anaesthetic bound is also related to the octanol: water partition coefficient as mentioned above.
2. Niiya et al (14) - Pre-treatment of pigs with ILE prevented hypotension by an amiodarone infusion. This was due to amiodarone being sequestered to a great extent in the lipid emulsion compartment as seen in the ultra-centrifuged plasma samples.
3. Weinberg et al(15) – Blood samples analysed from rats resuscitated from bupivacaine toxicity using vasopressin versus lipid treatment, showed that the lipid group resulted in lower aqueous phase content of bupivacaine, lower myocardial content as well as an improved cardiac function.

**Indirect evidence:**

It was shown by Weinberg et al (16) that radio-labelled bupivacaine was cleared from the myocardium of isolated rat hearts infused with lipid emulsion more rapidly than in control specimens infused with saline. It has also been shown that the toxicity of an array of highly lipophilic drugs with different mechanisms and sites of action have been reversed with ILE. The high lipophilicity is indicated by a log P value (octanol: water partition coefficient) greater than two. Another indirect measure of this is the fact the both neurologic and cardiovascular toxicity are reversed by ILE (17).

**Alternative mechanisms**

Ongoing research has led to an improved (yet incomplete) understanding of the mechanism underlying ILE. Thus far, the mechanisms of ILE has been described as multimodal; having effects *intravascularly* (lipid sink, lipid shuttle), *intracellularly* (metabolic , protein signalling) and on the *membrane* (ion channels) (17). In addition, direct cardiac effects of ILE are being explored as a contributing factor and will be discussed. The lipid sink theory could not sufficiently explain the mechanism of resuscitation by ILE. The action of ILE was much faster than expected based on the lipid sink theory alone. This was shown in a physiologically based pharmacokinetic model study (12, 18) and indicated that the possibility of other mechanisms should be sought.

**Intravascular**

It was also shown that lipid emulsions don't permanently sequester lipophilic agents but rather accelerate the redistribution of these drugs away from susceptible organs such as the brain and heart, to be stored, metabolised and excreted (19). In this way recovery from toxicity was facilitated by redistribution rather than just a lipid sink effect. This effect has improved the understanding from a lipid sink to rather a *lipid shuttle* mechanism, where the capture and release of lipophilic drugs can account for reversal of toxicity. This also emphasises the need for continued high quality resuscitative measures (19).

**Metabolic**

One of the mechanisms of local anaesthetic cardiotoxicity is impaired fatty acid metabolism in the cardiac myocytes i.e. impaired cardiac myocyte mitochondrial metabolism and inhibiting ATP synthesis. Stehr et al (20) showed that lipid infusion plasma levels too low to cause a lipid sink effect in isolated rat hearts, caused a direct inotropic effect after local anaesthetic induced cardiac depression. In another animal study (21) supporting the metabolic theory, the steps leading to cellular apoptosis (by inhibition of mitochondrial permeability transition pores (mPTP) from opening) was attenuated with ILE.

**Ion channel effects**

1. *Calcium hypothesis* – The was based on the initial study using Guinea pig ventricles, showing that fatty acids induce an influx of calcium into cardiac myocytes resulting in a positive inotropic effect. This theory was contested when studies done later showed that in fact fatty acids inhibited calcium influx into cardiac myocytes(19).

2. Free fatty acids have been shown to reduce the inhibition of cardiac sodium channels by bupivacaine (22). The ILE may displace the bupivacaine from cardiac sodium channels reducing the toxic effects.

**Direct cardiac effects**

The direct cardiac effects of ILE were demonstrated in studies under conditions of drug toxicity as well as under non-toxic conditions. Fettiplace et al (23) showed that in rats anaesthetised with isoflurane (and in isolated rat hearts), that ILE had a direct cardiotonic effect (positive inotropy and lusitropy) under non-toxic conditions. They then hypothesized that the inotropic effect of ILE could be a contributing factor in reversing cardiotoxicity secondary to drug overdose. Overall the exact mechanism of improved cardiac output is still unclear.

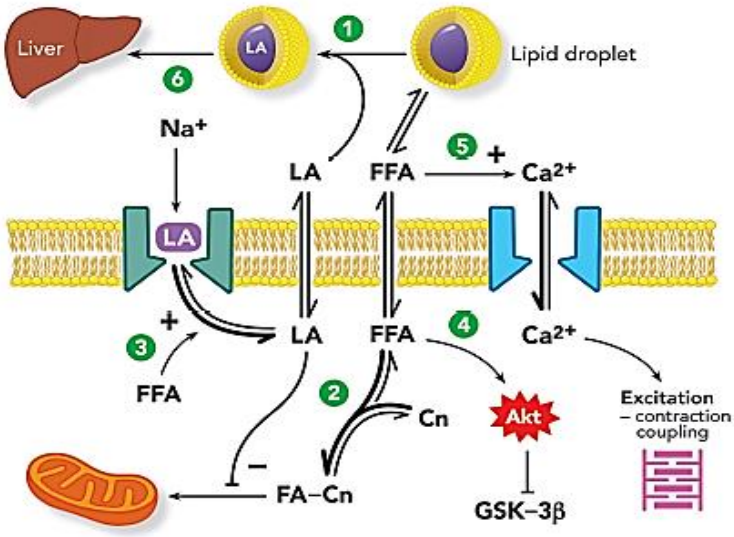


Fig. 1. Proposed mechanisms of lipid resuscitation. After infusion, the lipid emulsion exists in the blood as emulsified oil droplets or multilamellar vesicles. (1) Capture of local anesthetic (lipid sink); (2) Increased fatty acid uptake by mitochondria (metabolic effect); (3) Inteference with local anesthetic binding of sodium channels (membrane effect); (4) Activation of Akt cascade leading to inhibition of GSK-3β (cytoprotection); (5) Promotion of calcium entry *via* voltage-dependent calcium channels (ionotropic/ inotropic; can also involve mitochondrial calcium dynamics); (6) Accelerated shunting (pharmacokinetic effects). Akt – a serine/threonine protein kinase important in cell survival, proliferation, and migration, also called protein kinase B; $Ca^{2+}$ – calcium ion; Cn – carnitine; FA-Cn: fatty acyl carnitine; FFA – free fatty acids; GSK-3β – glycogen synthase kinase (phophorylates and thereby inhibits glycogen synthase; inhibition of GSK-3β has been implicated in preventing myocardial ischemia–reperfusion injury); LA – local anesthetic; $Na^{+}$ – sodium ion.

**Figure 4:** Six mechanisms of lipid resuscitation in LAST(17)

**Controversies**
**Adrenaline use**

The use of adrenaline in cases of cardiac arrest makes the management of LAST difficult. Many human cases and animal studies show that adrenaline does not successfully treat cardiovascular collapse in the setting of LAST. For this reason animal studies (predominantly rodent models) have focused on the use of vasopressors in LAST, comparing the use of adrenaline to ILE and the effects of combining both in resuscitation. Findings have shown that ILE is superior to adrenaline use in the resuscitation of LAST (24) and that adrenaline use may be detrimental if given in high doses when used with ILE.

It also impaired lipid resuscitation from bupivacaine cardiotoxicity resulting in worse outcomes(25). The adverse effects of adrenaline include the intense vasoconstriction which can worsen tissue hypoxaemia, stimulating lactate production and worsening acidosis, arrhythmogenicity as well as increasing myocardial oxygen consumption. It follows suit that these effects may compound the cardiotoxicity of local anaesthetic overdose. Weinberg et al conducted studies in rat models of bupivacaine-induced asystole and demonstrated that ILE is superior to adrenaline, vasopressin or the combination of both vasopressors for measured haemodynamic variables at 10 minutes (9).

## Dosing and Timing

Optimal dosing is not yet clear but official regulatory bodies have recommended an initial bolus dose of 1.5ml/kg of 20% lipid emulsion followed by a continuous infusion 0.25-0.5ml/kg/min of 20% lipid emulsion. As per the FDA and the recommendations on the package insert of Intralipid, this keeps the daily dose below 2.5g fat/kg (12.5 ml/kg 20% lipid emulsion), above which increased frequency of complications occur. It has been suggested that lower doses (0.25ml/kg/min of the infusion may reduce complication associated with higher infusion rates). When to administer ILE? Most case reports show that practitioners administer ILE only once traditional resuscitation has failed. However, early administration may improve outcomes.

## NON LOCAL ANAESTHETIC DRUG TOXICITY

The mounting evidence in animal studies and human case reports of lipid resuscitation in LAST, expanded into the use of ILE in resuscitation of other lipophilic drug overdose. The first case (26) reported using ILE for the management of a non-local anaesthetic drug toxicity, was a significant lamotrigine and bupropion overdose by an adolescent patient. The patient suffered a cardiac arrest and was non responsive to resuscitation for 90 minutes. An anaesthesiologist suggested the use of ILE and the patient responded to it after a single bolus. Subsequently, a wide range of lipophilic drug toxicities have been treated successfully with ILE. These include beta blockers, calcium channel blockers, a variety of psychotropic agents, parasiticides and herbicides(17). Most of the drugs tested in animal studies are lipophilic in nature and structurally similar to local anaesthetics which may account for the successful resuscitations.

Case series (18),(17), (19),(27) report an improvement and reversal of both neurological and cardiovascular dysfunction. However, this evidence is confounded by cases of multiple drug overdose where it becomes difficult to delineate which drug toxicity was being treated if more than one agent was lipophilic in nature. Although only case reports and case series form the backbone of the human evidence available in managing toxicity of this complex nature, they provide insight into the benefits that ILE may provide, including reducing morbidity and mortality and the associated cost burden on the health system. Animal studies provide valuable information but cannot be translated to humans.

Ethical reasons prohibit more reliable analysis in the form of human randomised controlled trials; therefore we can only rely on responsible unbiased case reporting and animal studies. All clinicians are encouraged to come forward to share their experience with the international medical community via forums such as online resources:

1. www.lipidrescue org
2. www.lipidregistry.org

The American College of Medical Toxicology Position Statement on the use of ILE ~~i~~s that the decision to use ILE in non-local anaesthetic drug toxicities must be made by the treating physician. They also noted that it is reasonable to use ILE in cases of lipophilic drug overdose with any physiological instability, even without cardiac arrest occurring.

## ADVERSE EFFECTS OF INTRAVENOUS LIPID EMULSION ADMINISTRATION

Outside of nutritional support, the more recent role of ILE in resuscitation from drug toxicity has increased the frequency of its use. Coupled with increased use are the adverse effects of intravenous lipid therapy, which can occur with its use in nutrition and as an antidote. When the body cannot clear the exogenous lipid load, accumulation of ILE occurs. It is usually well tolerated in doses of 1-2g/kg/day.

Complications associated with the use of ILE (28),(29),(5),(27)

| Complication | Comment |
|---|---|
| Lipaemia induced interference with laboratory studies | The most common problem with ILE. Difficulty analysing blood gas, haematological and biochemistry samples. This leads to delays in diagnosis and management of electrolyte abnormalities in critically ill patients. This is despite ultracentrifugation of samples. The time period of interference in one case series (27) was between 6-20 hours. |
| **Gastrointestinal System**<br>Acute pancreatitis | It may be linked to hypertriglyceridemia (>1000mg/dl). Association of Anaesthetists of Great Britain and Ireland (AAGBI) recommends monitoring of the patient post ILE therapy for development of pancreatitis |

| Complication | Comment |
|---|---|
| Hepatosplenomegaly<br>Liver dysfunction<br>Cholestasis | <br><br>Jaundice |
| **Immune System**<br>Immunological dysfunction<br><br>Increased risk for infection<br><br>Allergic reactions | Impaired reticuloendothelial system function with immunomodulatory effects, potentially pro<br>Inflammatory<br><br>Risk of microbial growth within emulsions<br><br>Especially with soybean formulations |
| **Pulmonary dysfunction** | Thought to be caused by hyperlipidaemia and may be reduced by reducing the rate of infusion. They may cause pulmonary vasoconstriction, part of a fat embolism syndrome |
| **Coagulopathies**<br>Resistance to warfarin therapy | |
| **Lipid Metabolism**<br><br>Hypertriglyceridaemia<br><br>Fat emboli<br>Fat overload syndrome | <br><br>Large lipid load cannot be cleared by lipoprotein lipase and accumulates in the body |
| Paediatrics | Deaths premature and small for gestational age infants have been reported linked to fatty infiltration of the lungs. The impaired ability to clear lipids makes monitoring of triglycerides prudent and as well as not exceeding the daily dose (<1g fat/kg/4 hours) and using slow infusion rates |
| Thrombophlebitis | |
| Seizures | |

## CONTRAINDICATIONS

ILE should not be administered in patients with disturbances of normal fat metabolism such as pathologic hyperlipidaemia, lipoid nephrosis or acute pancreatitis if accompanied by hyperlipidaemia (30). Caution must be taken with patients suffering from liver disease, and liver enzymes should be monitored.

## CONCLUSION

Lipid emulsions are continuously being investigated. With improved skills in regional anaesthesia techniques, increasing popularity of ultrasound guided techniques, and the increasing knowledge of the adverse effects of intravenous/inhalational anaesthetic agents, regional anaesthesia provides an attractive option for managing our patients. Knowing this, local anaesthetic drug toxicity will always be a danger. All medical practitioners need to be aware of the development of ILE, its uses and how to administer it. Its role in the emergency department and critical care with the management of serious lipophilic drug toxicity in such a wide variety of agents is an exciting area of research. The evidence for drug toxicity resuscitation is not of a high level and the use of ILE for this indication still remains “off label”. The potential lifesaving properties of ILE need to be balanced with the associated complications. The future holds much promise regarding the role of ILE in myocardial protection and novel ways of drug delivery e.g.: emulsified volatile agents as well as liposomal formulations of hydrophilic drugs.

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