

# Lipid emulsion therapy: non-nutritive uses of lipid emulsions in anaesthesia and intensive care

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Lipid emulsions were introduced into clinical practice more than five decades ago as a calorically dense, non-glucose-based energy source for parenteral nutrition. Recently, intravenous lipid emulsions have been used as rescue for systemic local anaesthetic toxicity. However, the non-nutritive, therapeutic roles of lipid emulsions have recently expanded. This review considers these newer uses of lipid emulsions as drug administration vehicles, for treatment of lipophilic drug toxicity, and as modifiers of ischaemia-reperfusion injury in the anaesthetic and critical care environments. The potential adverse effects of lipid emulsion administration are also succinctly addressed.

**Keywords:** Intralipid<sup>®</sup>, ischaemia-reperfusion injury, lipid emulsions, local anaesthetic toxicity, propofol

## Introduction

Lipid emulsions were introduced into clinical practice more than five decades ago as a calorically dense, non-glucose-based energy source for parenteral nutrition. Recently, these emulsions have been employed as 'lipid rescue' for systemic local anaesthetic toxicity.<sup>1</sup> However, the non-nutritive therapeutic roles of lipid emulsions have recently expanded. These include their use as drug carrier vehicles, for management of lipophilic drug toxicity and as an exciting new adjuvant for the management of myocardial ischaemia-reperfusion injury (see Table 1).

Arvid Wretling of the Karolinska Institute, Sweden devoted years solving the toxicity associated with previous intravenous fat solutions.<sup>2</sup> This culminated with the 1962 introduction of Intralipid<sup>®</sup> (Fresenius Kabi, Bad Homburg, Germany), an emulsion comprising soybean oil, egg phospholipid, and glycerin (Table 2). Intralipid<sup>®</sup> is currently manufactured with lipid concentrations of 10, 20 and 30%, these being commonly used as a drug carrier vehicle, 'lipid rescue', and the formulation of parenteral nutrition, respectively.<sup>3</sup>

Table 1: Therapeutic roles of lipid emulsions

1. Parenteral nutrition
2. Drug carrier vehicle
3. Resuscitation from lipophilic drug toxicity
4. Reperfusion injury attenuation

Table 2: Intralipid<sup>®</sup> constituents

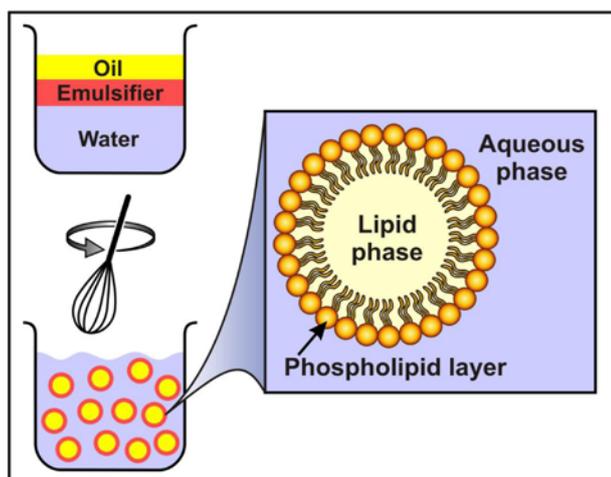
1. 20% Soybean oil
2. 1.2% Egg yolk phospholipids
3. 2.25% Glycerine
4. Sodium hydroxide
5. Water

## Understanding emulsions

An emulsion is defined as any mixture of liquids that do not normally mix.<sup>4</sup> An emulsion is formed by small liquid droplets being dispersed in a second liquid.<sup>5</sup> The small droplets and the liquid into which they are dispersed are referred to as the discontinuous and continuous phases respectively. Therapeutic lipid emulsions are typically lipid droplets suspended in water; therefore the discontinuous and continuous phases are usually lipid and aqueous phases respectively (Figure 1).<sup>5</sup> Inspection of an oil-and-vinegar salad dressing after it has stood for a while emphasises the inherent tendency of lipids to coalesce. To stabilise mixtures and prevent this from happening, emulsifiers are added to emulsions.<sup>7</sup> Emulsifiers are both fat and water soluble, and a single molecular layer of the emulsifier arranges itself around the lipid droplet, surrounding it (Figure 1).<sup>7</sup> Phospholipids such as egg lecithin are commonly used as emulsifiers. For example, when egg is added to stabilise the oil-and-vinegar mixture, the emulsion is known as mayonnaise.

Therapeutic lipid emulsions may be described as oil-in-water macroemulsions, with a droplet diameter between 0.1 and 100 microns.<sup>6</sup> The droplets are of similar shape and size to physiological chylomicrons, and are metabolised in a similar manner. These lipid droplets are large enough to reflect white light, which gives them their typical solid, milky appearance.<sup>6</sup> Indeed, the word 'emulsion' originates from the Latin 'mulgere' meaning 'to milk out'.

The fatty acids (lipid phase) of lipid emulsions may originate from soya beans, safflower, coconut, olive, or fish oils.<sup>5,8</sup> The origin of the fatty acids is important as it determines the ratio of medium- to long-chain triglycerides. This ratio imparts the emulsion with particular physiological qualities and also its side effect profile. Long-chain triglycerides are a rich source of essential omega-6 and omega-3 polyunsaturated fatty acids. Unfortunately, long-chain triglycerides are pro-inflammatory. They accelerate lipid peroxidation with deleterious effects on neutrophil function while their increased rate of arachidonic acid production aggravates pro-inflammatory cytokine production.<sup>8</sup> Medium-chain triglycerides are more stable and incur fewer immune modulatory and



Note: Magnification: Lipid droplet portraying monolayer of phospholipid as emulsifier, which separates the interior lipid phase from the exterior aqueous phase. See text for discussion.

Figure 1: The making of a lipid emulsion.

Table 3: Lipid emulsion preparations available for clinical use

Name	Fatty acid composition	Emulsifier
Intralipid®	100% soybean oil	Egg phospholipid
Lyposin II®	50% soybean oil; 50% safflower oil	Egg phospholipid
Lyposin III®	100% soybean oil	Egg phospholipid
Lipofunden MCT®Medialipide®	50% soybean oil; 50% coconut oil	Egg phospholipid Sodium oleate
Structolipid®	64% soybean oil; 36% coconut oil	Egg phospholipid
Omegaven®	100% fish oil	Egg phospholipid
Lipoplus®	50% coconut; 40% soybean; 10% fish oil	Egg phospholipid
ClinOleic®	80% olive oil; 20% soybean oil	Egg phospholipid Sodium oleate
SMOFlipid®	30% coconut oil; 30% soybean oil; 25% olive oil; 15% fish oil	Egg phospholipid Sodium oleate

Note: LCT: Long chain triglyceride; MCT: Medium chain triglyceride.

inflammatory side effects. However, they undergo faster metabolism and incur the costs of increased energy expenditure, body temperature, and ketosis formation.<sup>8</sup> Therefore, medium- and long-chain triglycerides are always combined, in an attempt to conserve caloric value, while minimising the side effects.<sup>8</sup>

Various lipid emulsion preparations currently available for clinical use, with their associated fatty acid composition and corresponding emulsifier, are set out in Table 3.<sup>5,7,9</sup> The interested reader is referred to detailed reviews of the physicochemical properties and fatty acid composition of lipid emulsions by Waitzberg and colleagues,<sup>5</sup> and Hippalgaonkar and colleagues.<sup>8</sup>

### Lipid emulsion as a drug carrier

Lipid emulsions are useful carrier vehicles for lipophilic drugs.<sup>8</sup> Lipid emulsions are used to deliver drugs to or via the skin (transdermal administration), to the eye, as well as parenterally. Propofol, etomidate, diazepam, amphotericin B, alprostadil (PEG<sub>1</sub>), dexamethasone, and certain vitamins (A, D<sub>2</sub>, E, K<sub>1</sub>) are examples of intravenous drugs formulated as emulsions.<sup>10</sup> Intravenous formulations that use lipid emulsions as carrier vehicles have distinct advantages and disadvantages (Table 4). Two serious, underappreciated potential problems are emulsion instability and microbial contamination.

### Emulsion instability

To exert an effect following intravenous administration, the lipid soluble drug must diffuse across the phospholipid emulsifier

into the blood.<sup>6</sup> The rate at which the drug will diffuse out of the lipid droplet is governed by the principles encompassed by Fick's law, namely the concentration gradient across the lipid droplet membrane, the respective partition coefficients of the drug within the fat and aqueous states, and the surface area of the drug-containing lipid droplet. The single molecular layer emulsifier surrounding the lipid droplet slows the rate at which the free drug becomes available when compared with drugs formulated as aqueous solutions.

Oil-in-water macroemulsions are inherently unstable. Flocculation, coalescence and creaming (see Table 5) are a result of attraction between the lipid droplets and occur naturally in any lipid emulsion.<sup>6,11</sup> Should lipid droplet size increase due to coalescence, the concomitant decreased surface area will further slow the rate of diffusion of drug into the blood with altered drug pharmacokinetics.<sup>6,11</sup> This stresses the importance of emulsion stability.

Flocculation and creaming can be reversed to some extent by gently shaking the ampoules before use.<sup>6,11</sup> However, irreversible

emulsion instability (severe coalescence) can be a consequence of extreme agitation, temperature variation and alteration of the aqueous phase. Adding charged substances to the formulation (e.g. dilution with lignocaine, water, or normal saline) causes disruption of the negatively charged, mutually repelling droplet surfaces. This incites adhesion and coalescence with a tenfold or greater increase in droplet size, which may result in pulmonary, splenic, placental, and cerebral microembolisation.<sup>12,13</sup> Only high shear homogenisation with re-filtration will ensure reversal of emulsion degradation of this severity. Mixing or diluting propofol, or for that matter any drug formulated as a lipid emulsion, is therefore strongly discouraged.<sup>6</sup>

### Microbial growth medium

The high nutritive value of lipid emulsions promotes microbial growth after extrinsic contamination. Soon after the clinical introduction of propofol, cases of unexpected postoperative infections occurred.<sup>14-16</sup> Propofol 1%, without an antimicrobial agent added, support the growth of various bacteria and fungi, including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*.<sup>17-20</sup> For this reason, preservatives are commonly added to propofol. Only ethylenediaminetetraacetic acid (EDTA) and metabisulfate are currently approved by the Food and Drug administration.<sup>6</sup> They have been successfully incorporated into propofol without deleteriously altering either the emulsion stability or its pharmacokinetic profile.<sup>6</sup> Despite the preservatives being effective enough to inhibit microbial

Table 4: Advantages and disadvantages of lipid emulsions as carrier vehicle for specific drugs<sup>6,8</sup>

Advantages	Disadvantages
1. Reduction of <i>injection pain, irritation and thrombophlebitis</i> of diazepam, etomidate and clarithromycin formulations	1. <i>Emulsion instability</i> *
2. <i>Less nephrotoxicity and haemolysis</i> associated with amphotericin B preparation	2. <i>Hyperlipidaemia</i> : liposomes (droplets smaller than 0.08 micron) inhibit lipolysis and stimulate cholesterol synthesis
3. <i>Improved stability and solubility</i> with the sodium phenobarbital, clarithromycin, <i>all-trans-retinoic acid</i> and physostigmine preparations due to decreased susceptibility to oxidation and hydrolysis	3. <i>Microbial growth medium</i> *
4. Lipid emulsion formulations incorporating apo lipoprotein E in the phospholipid layer demonstrate a 70% increased hepatic uptake. This can provide <i>targeted drug delivery</i> in certain chemotherapeutic drugs	

\*See text for detailed discussion.

Table 5: Definition of terms defining lipid emulsion instability

**Flocculation:** Attractive forces overcome repulsive forces, resulting in droplet adherence

**Coalescence:** The thin film of surfactant between two flocculated droplets ruptures, resulting in mixing of the lipid phase; a larger, emulsified droplet is created

**Creaming:** As coalescence continues, droplet size increases and rises to the surface

growth to levels similar to non-lipid formulation, strict asepsis is mandatory.<sup>6</sup> This is specified as careful aseptic handling of propofol during preparation, single-patient use per ampoule, and the use of the ampoule within 6 h of breaking the seal.<sup>21</sup>

### Propofol

In its pure form, propofol is a yellowish oil that freezes at only 19°C. 2,6-di-isopropylphenol's poor water miscibility is due to its highly lipophilic benzene ring and its single ionisable group. Indeed, the only suitable vehicles for propofol are lipophilic substances or organic solvents, the latter being toxic to humans.<sup>6</sup> A miscellar emulsion of propofol and Cremophore EL underwent early, extensive human testing. This formulation was never marketed as it caused severe injection pain, a high incidence of anaphylaxis, and there were reports of associated peripheral neuropathy.<sup>6</sup> Thus, despite its therapeutic potential as an anaesthetic having been discovered decades earlier, it was only in the 1980s that emulsion technology could produce a stable and physiologically compatible propofol preparation.<sup>6</sup> Interestingly, propofol prepared as an emulsion exhibits greater potency, a smaller volume of distribution, less first-pass lung sequestration, and a decreased time to peak EEG effects when compared with equipotent doses of propofol in lipid-free formulations.<sup>6</sup>

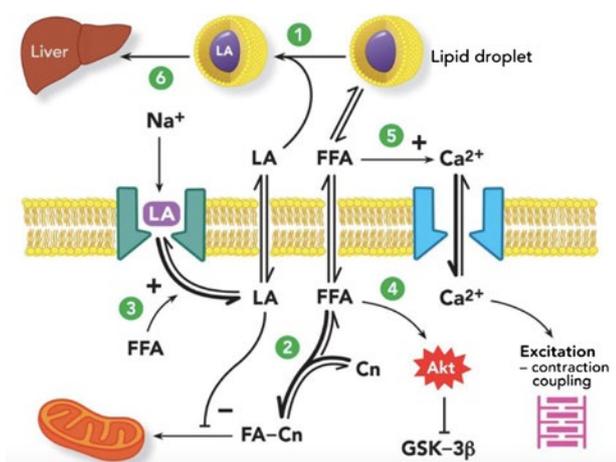
Recent technological advances have resulted in the development of propofol nano-emulsions (Microfol™, NanoMedex Pharmaceuticals, Wisconsin, USA) with droplets less than 0.1 micron in diameter.<sup>22,23</sup> Such nano-emulsions are colourless as droplets of this size do not reflect light. The decreased droplet size is associated with greater emulsion stability and less injection pain as there is less free aqueous phase propofol. Unlike current formulations, the propofol nano-emulsion is antimicrobial as the nanoparticles fuse with microbial membranes, causing pathogen lysis.<sup>22</sup>

### Emulsified isoflurane

A promising development over the past fifteen years is isoflurane in a lipid emulsion.<sup>24</sup> Animal studies have demonstrated rapid onset of general anaesthesia with intravenous, intraperitoneal, and even oral administration of emulsified isoflurane. A recent (unpublished) phase 1 clinical trial<sup>24</sup> demonstrated a predictable onset of unconsciousness within 40 s after starting an intravenous infusion. Recovery after discontinuation of the intravenous infusion is via respiratory elimination of the isoflurane. In this respect, analysis of end-tidal isoflurane partial pressures would be a valid estimate of effect-site concentration of an intravenously administered agent. Emulsified isoflurane also has the potential to be utilised for regional anaesthesia as it has successfully been used in establishing epidural anaesthesia in rabbits,<sup>25</sup> subarachnoid anaesthesia in Beagle dogs,<sup>26</sup> and intravenous regional anaesthetic in rat tails.<sup>27</sup> There are additional benefits of emulsified isoflurane when employed in regional anaesthesia: it increases lignocaine's convulsion threshold<sup>28</sup> and when combined with lignocaine was synergistic in intravenous regional anaesthesia.<sup>27</sup>

### Lipid emulsion for treatment of drug overdose

The discovery-hypothesis that lipid emulsion is an effective treatment for local anaesthetic systemic toxicity (LAST) originated in Guy Weinberg's Chicago laboratory in 1998.<sup>29</sup> The first successful human lipid emulsion resuscitation following LAST was reported in 2006.<sup>30</sup> Subsequent case reports have described successful resuscitation of LAST from neonates to geriatrics, the oldest survivor being 92 years of age. These case reports have established the superiority of lipid resuscitation over vasopressor in LAST resuscitation,<sup>31</sup> early administration thereof attenuating LAST progression.<sup>32</sup> Successful lipid rescue has followed local anaesthesia toxicity involving bupivacaine,<sup>30,33</sup> ropivacaine,<sup>34,35</sup> mepivacaine,<sup>35,36</sup> and lignocaine.<sup>35,37</sup> Although Intralipid® has been most commonly used,<sup>31</sup> successful resuscitation from LAST has followed the use of other lipid emulsions such as SMOFlipid in pigs,<sup>38,39</sup> Liposyn III following bupivacaine induced cardiac arrest,<sup>40</sup> and Medialipid.<sup>41</sup> Despite the 20% greater binding efficacy of long- compared with medium-chain triglycerides,<sup>42</sup> Clinoleic® and Intralipid did not bind ropivacaine or bupivacaine differently.<sup>43</sup> Therefore, the choice of lipid emulsion probably does not make a difference in the emergency situation — just use it! The management of LAST or other lipophilic drug toxicity is beyond the scope of this article. The reader is referred to <http://www.asra.com>, [www.tandfonline.com/ojaa](http://</a></p>
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Note: 1. *Partitioning effect* also termed the 'lipid sink' effect: capturing of local anaesthetic molecules inside the lipid droplet. 2. *Metabolic effect*, also termed the 'lipid flux' effect: increased fatty uptake by mitochondria. 3. *Membrane effect*: direct interference of local anaesthetic binding to sodium channels by lipid emulsion. 4. *Cytoprotective effect*: activation of Akt cascade leading to inhibition of GSK-3 $\beta$ . 5. *Promotion of calcium entry* via voltage-dependent calcium channels, promoting myocardial excitation-contraction coupling. 6. *Pharmacokinetic effect*: accelerated hepatic 'shunting' of bupivacaine. Source: With permission: Wolter Kluwers Health Inc. From: *Lipid emulsion infusion: resuscitation for local anesthetic and other drug overdose*.<sup>31</sup> Akt = a serine/threonine protein kinase important in cell survival, proliferation, and migration, also called protein kinase B; Ca<sup>2+</sup> = calcium ion; Cn = carnitine; FA-Cn = fatty acyl carnitine; FFA = free fatty acids; GSK-3 $\beta$  = glycogen synthase kinase (phosphorylates and thereby inhibits glycogen synthase; inhibition of GSK-3 $\beta$  has been implicated in preventing myocardial ischemia-reperfusion injury); LA = local anaesthetic; Na<sup>+</sup> = sodium ion.

Figure 2: Proposed mechanisms of lipid resuscitation

[www.lipidrescue.org](http://www.lipidrescue.org), and <http://www.aagbi.org> for up to date information and useful checklists.

The first successful lipid-facilitated resuscitation following overdose with non-local anaesthetic, lipophilic drugs (a combination of bupropion and lamotrigine) was reported two years after the first LAST 'Lipid Rescue'.<sup>44</sup> Subsequent case reports have endorsed lipid emulsion efficacy in treating overdoses of lipophilic drugs such as calcium channel blockers,  $\beta$ -blockers, psychotropics, tricyclic antidepressants, selective serotonin reuptake inhibitors, antiarrhythmic, and overdoses involving multiple, unknown drugs.<sup>35,45</sup> It is important to appreciate that propofol contains insufficient lipid emulsion to be used as therapy in local anaesthetic or other lipophilic drug toxicity.

Weinberg's group has hypothesised six mechanisms whereby lipid emulsion therapy is effective in LAST (Figure 2).<sup>31</sup> Evidence is mounting in support of some of these proposed mechanisms with considerable backing for the 'lipid sink' and 'lipid flux' theories.

The 'lipid sink' or 'partitioning' effect presumably works by capturing lipophilic drugs in the lipid portion of the emulsion. There is both direct and indirect evidence for this mechanism. The indirect evidence includes:

- Reversal of LAST-induced neurological symptoms has been achieved with lipid emulsion administration, despite the brain not readily utilising fatty acids for energy.<sup>31</sup>
- Lipophilicity is the only discernible common characteristic explaining the variety of drug overdoses successfully resuscitated with lipid emulsions.<sup>31</sup>
- Radiolabelled bupivacaine levels decline more rapidly in lipid-perfused rat hearts, compared with the lipid-free control groups.<sup>46</sup>

There is direct evidence that local anaesthetics, amiodarone and other lipid-soluble drugs are partitioned into the lipid phase:

- Mazoit et al.'s *in vitro* study demonstrated that large amounts of local anaesthetic agents bind to lipid emulsion.<sup>42</sup>
- Weinberg et al. analysed blood samples from one of their rat studies comparing vasopressin with Intralipid® resuscitation of LAST.<sup>47</sup> Bupivacaine was present in far higher concentrations in the aqueous phase of the vasopressin than the lipid emulsion group.
- Niiya et al. pre-treated pigs with lipid emulsion prior to inducing amiodarone 'toxicity'.<sup>48</sup> The lipid-treated group demonstrated less hypotension. Furthermore, after plasma ultracentrifugation, higher amiodarone levels were measured in the lipid phase.
- Samuels et al. examined the validity of the lipid sink effect using an innovative model.<sup>49</sup> They studied the effects of lipid emulsion therapy on four drugs, which each caused methaemoglobinaemia. Each drug was uniquely lipid soluble. The measurement of methaemoglobin concentrations represented an accurate, easy to measure endpoint. They hypothesised and clearly demonstrated that the more lipid soluble the drug, the more effective lipid emulsion therapy was in reducing methaemoglobin concentrations. Their conclusions strongly support the lipid sink theory.
- French et al. studied 11 drugs associated with successful lipid emulsion resuscitation.<sup>50</sup> After adding Intralipid® to serum, they investigated drug partitioning between serum and the lipid emulsion. The ability of lipid emulsions to extract drugs from the circulation was directly related to the drug's lipophilicity.

Robust evidence also supports the 'metabolic' or 'lipid flux' effect. Stehr et al. demonstrated reversal of bupivacaine-induced cardiomyocyte dysfunction at lipid emulsion levels too low to sequester bupivacaine from the circulation.<sup>51</sup> Further support for the metabolic theory is that following inhibition of cardiomyocytes' ability to oxidise fatty acids, lipid emulsion therapy cannot reverse bupivacaine cardiotoxicity.<sup>52</sup>

### Lipid emulsion as a therapy for ischaemia-reperfusion injury attenuation

A potentially groundbreaking role of lipid emulsions is as an agent to attenuate ischaemia-reperfusion injury. During ischaemia, anaerobic cardiomyocyte metabolism results in lactate production, decreased intracellular pH, and intracellular calcium overload.<sup>53</sup> Following reperfusion, electron transport chain reactivation produces reactive oxygen species that cause injury by three mechanisms:

- (1) attraction of neutrophils to injured cardiomyocytes;
- (2) aggravation of sarcoplasmic reticular dysfunction with further increases in cytosolic calcium; and
- (3) facilitating mitochondrial permeability transition pore opening.<sup>53</sup>

Opening of the mitochondrial permeability transition pore results in solute and free water influx, which ultimately leads to mitochondrial lysis. Upon rupturing, many pro-apoptotic factors usually isolated in the mitochondrial intermembranous space are released into the cardiomyocyte cytosol. This mechanism represents one of the main drivers of myocyte apoptosis (Figure 3). Lipid activates the reperfusion injury salvage kinase (RISK) pathway, which, in turn, activates the protein kinase B (Akt) and

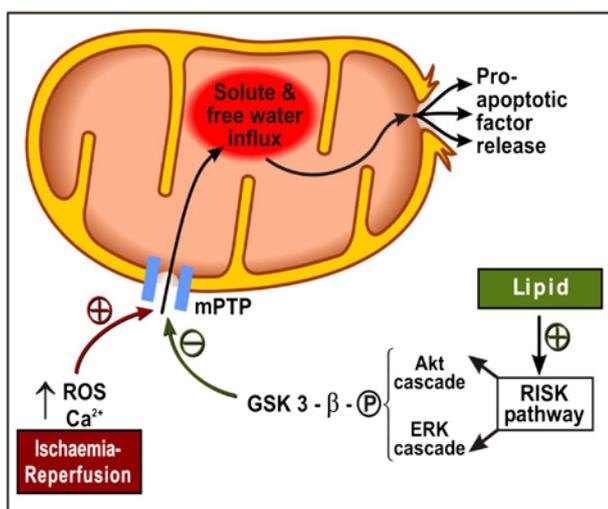
extracellular signal-regulating kinase (ERK) cascades.<sup>54,55</sup> Both pathways converge to phosphorylate glycogen synthase kinase 3- $\beta$  (GSK 3- $\beta$ ). Glycogen synthase kinase 3- $\beta$  inhibits the opening of the mitochondrial permeability transition pore with less apoptosis (see Figure 3).

Rahman *et al.*'s recent, pioneering work demonstrated that lipid emulsion was protective of the myocardial following ischaemia-reperfusion damage.<sup>54</sup> The mechanisms elucidated by this study included:

- (1) Lipid-emulsion-initiated *preconditioning* as a 70% decrease in infarct size was observed if lipid emulsion was administered prior to reperfusion.
- (2) Lipid emulsion administered *at reperfusion* improved functional recovery and decreased infarct size.
- (3) Lipid emulsion appeared to initiate *postconditioning* as the cardioprotection was sustained for a time after terminating the infusion.

Similar results have been shown in two other publications.<sup>55,56</sup> Lipid emulsion treatment improved contractility following ischaemia reperfusion in isolated mouse cardiomyocytes.<sup>57</sup> Interestingly, emulsified isoflurane exhibits a potent, pre- and post-conditioning effect in animal ischaemia-reperfusion models of cardiomyocytes,<sup>58,59</sup> kidney,<sup>60</sup> brain,<sup>61</sup> lung and liver<sup>62</sup> cells, future work in this field being eagerly awaited.

Although promising, many questions need answering before lipid emulsion therapy is hailed as the new 'magic bullet' in cardioprotection.<sup>63</sup> For example, the exact chemical compound responsible for these protective effects is not yet known. Furthermore, all work until now has been performed in rats, ex vivo Langendorff mouse heart models, or isolated muscle preparations. Therefore, a question that needs addressing is whether these *in vitro* experiments can be reproduced in animals, and eventually in humans.



Note: This diagram depicts the central role of the mitochondrial permeability transition pore (mPTP) in ischaemia-reperfusion injury and demonstrates the pathway whereby lipid emulsions attenuate it. ROS = reactive oxygen species; Ca<sup>2+</sup> = intracytosolic calcium concentration; mPTP = mitochondrial permeability transition pore; GSK 3- $\beta$  - P = Phosphorylated glycogen synthase kinase 3- $\beta$ ; Akt cascade = protein kinase B cascade; ERK cascade = extracellular signal-regulating kinase cascade; RISK = reperfusion injury salvage kinase.

Figure 3: Ischaemia-reperfusion injury and lipid emulsion

## Adverse effects associated with lipid emulsion infusions

Most case reports describe successful resuscitation with less than the recommended upper limit of 10 ml/kg of a 20% Intralipid® preparation.<sup>64</sup> This dose should be compared with the murine Intralipid® LD50 of 67.7  $\pm$  10.7 ml/kg. Complications following lipid emulsion administered as part of long-term parenteral nutritional are well known (Table 6).<sup>5,12,65-73</sup> Complications and concerns following acute administration of 'Lipid rescue' are starting to be investigated.<sup>74</sup>

The following should be taken into consideration:

- a. *Pharmacokinetic alterations*: Lipid-containing parenteral nutrition is well described to interfere with the pharmacokinetics of certain drugs.<sup>75</sup> It is currently not known whether intravenous lipid emulsion can deleteriously alter the bioavailability of important lipophilic resuscitation drugs such as amiodarone, lignocaine, beta-adrenoreceptor, and calcium channel blockers.
- b. *Effects of lipid emulsions on anaesthesia*: There is no knowledge on how lipid emulsions affect the depth of anaesthesia *per se*. Considering emulsified isoflurane and that propofol is dissolved in Intralipid®, this is an important but hitherto unaddressed question. The only available study reported that depth of anaesthesia increased in rats administered thiopentone and lipid emulsion concomitantly.<sup>76</sup>
- c. *Lipid anaphylaxis* could occur, especially in patients with nut or soybean sensitivity.<sup>71</sup>
- d. *Interference with laboratory and blood gas analysis* despite blood ultracentrifugation has been reported to occur for more than 12 h following Lipid Rescue. Haemoglobin and methaemoglobin results are increased, and electrolyte and base excess estimation are incorrect.<sup>64</sup> Such problems have created serious dilemmas regarding patient management and prevented one patient from becoming a transplant candidate.<sup>74</sup>
- e. *Pancreatitis* has been reported following lipid rescue. This had a strong temporal association with hypertriglyceridaemia, resolution occurring along with normalisation of the lipid profile.<sup>74</sup>

Table 6: Adverse effects associated with the long-term administration of lipid emulsions<sup>5,12,65-73</sup>

1. *Dyslipidaemia* (hypercholesterolaemia and hypertriglyceridaemia)
2. *Modulation of cell-mediated immunity*
3. *Increased inflammation*
4. *Increased oxidative stress*
5. *Fat emboli* (pulmonary, splenic, placental, cerebral)
6. *Reticulo-endothelial dysfunction*
7. *Thrombophlebitis* with peripheral administration
8. *Interference with laboratory results*
9. *Increased oxygen consumption*
10. *Increased shunt fraction and pulmonary artery pressure* in ARDS
11. *Anaphylaxis*
12. *Pancreatitis*

## Conclusion

The therapeutic roles of lipid emulsion have expanded far beyond the realms of nutrition. Many lipophilic drug solutions are formulated as lipid emulsions, including propofol. A serious and underappreciated disadvantage of these preparations is that of emulsion instability, which occurs when the preparations are diluted with charged solutions. Anaesthetists' future armamentarium may include emulsified isoflurane. Lipid emulsions have a well-established role in the management of local anaesthetic toxicity, as well as acting as an antidote in various other lipophilic drug overdoses. The evidence supporting the 'lipid sink' and the 'lipid flux' theories is growing in strength. Lipid emulsion therapy, both alone and in combination with isoflurane, has promising cytoprotective effects following ischaemia reperfusion in animals. Reported complications in patients receiving lipid rescue include pancreatitis, interference with laboratory results, and pharmacokinetic alteration of drugs used during lipid resuscitation.

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## Note

i. Fick's law of diffusion:  $V = \frac{A \cdot D \cdot (P_1 - P_2)}{t}$

where V is the rate of diffusion, A is the surface area available for diffusion, D is the diffusion coefficient, Solubility/ $\sqrt{\text{Molecular mass}}$ ,  $P_1 - P_2$  is the partial pressure difference governing diffusion, t is the thickness of the membrane or diffusion distance.

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