

## The use of intravenous lipid emulsion (ILE) as an antidote in drug toxicity – an update

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### Introduction

Intravenous lipid emulsion (ILE) has been used for parenteral nutrition in NHS hospitals for many years. There is now a new research finding of its role as an antidote for drug toxicity which is gaining popularity in clinical use. ILE is now recommended by Resuscitation Council of the United Kingdom for local anaesthetic-induced systemic toxicity, and is currently used worldwide. There are case reports of its successful use in the treatment of refractory cardiac arrests secondary to non-local anaesthetic drug overdoses. However, there is no agreed guidance on treating acute non-local anaesthetic poisonings with ILE.

The purpose of this review is to evaluate current literature regarding ILE therapy in drug toxicity, to provide clinicians with an understanding of the proposed mechanisms of action, and to improve awareness of the novel use of this drug.

### Background

The first safe fat emulsion for human use, with the brand name Intralipid, was invented by Professor Arvid Wretling of Sweden in 1962. Intralipid is formulated as an emulsion of soybean oil, purified egg phospholipids, anhydrous glycerol, sodium hydroxide and water for injection. It is widely used as a component of parenteral nutrition. It is available in 10%, 20%, and 30% concentrations. The 30% concentration is not approved for direct intravenous infusion, but should be mixed with amino acids and dextrose as part of a total nutrient admixture. Although Intralipid is the most commonly used lipid emulsion, other lipid emulsions such as Medialipid® and Liposyn® have been used successfully for lipid rescue.

In 1998, Weinberg et al published data indicating the effectiveness of Intralipid in treating experimental models of severe cardiotoxicity, secondary to intravenous overdose of local anaesthetic (LA)

drugs such as bupivacaine<sup>1</sup>. Their experimental model demonstrated that inducing cardiotoxicity was profoundly difficult in rats and dogs that had been pretreated with lipid<sup>2</sup>. Studies in rats and later in dogs, confirmed that animals given pre or follow-up treatment with lipids for bupivacaine overdose recovered remarkably well. This led to the trial of such therapy in patient management, and Rosenblatt et al reported the first clinical application of such therapy in 2006<sup>3</sup>. Since there was no antidote available for LA induced cardiac arrest, a trial of lipid emulsion was recommended after cardiopulmonary resuscitation (CPR), before giving up the resuscitative attempt<sup>4</sup>. Observations from case reports that followed showed a move forward from this advice, with lipid therapy started within minutes of diagnosis of local anaesthetic toxicity. Weinberg's experimental findings and the successive case reports, resulted in the Association of Anaesthetists of Great Britain and Ireland (AAGBI) recommending in August 2007 that lipid emulsion be immediately available in all areas where potentially cardio-toxic doses of local anaesthetics are given, along with guidelines for its use<sup>5</sup>. The use of Intralipid since then has been extended to the reversal of toxicity from other lipophilic drugs.

### Intravenous lipid emulsion (ILE)

Intravenous fat emulsion, in the form of Intralipid® 20% (Fresenius Kabi) has gained a wide usage in the treatment of local anaesthetic toxicity, a potentially fatal complication of regional anaesthesia or any procedure where local anaesthetics are administered. Intralipid 20% is presented as a white homogenous emulsion for intravenous infusion with a shelf life of up to 24 months. It has an osmolality of 350 mOsm /kg water and a pH of approximately 8. A 500ml bag is commonly used in the management of local anaesthetic toxicity. See figure 1 overleaf.

Intralipid is contra-indicated in disorders of

fat metabolism such as severe liver damage and acute shock. It is also contra-indicated in hypersensitivity to egg soya or peanut protein or to any of the active substances or excipients<sup>6</sup>.



**Figure 1**

### **Mechanism of action**

The exact mechanism of action of Intralipid as a drug antidote is unknown but the 'lipid sink' phenomenon, a term introduced by Weinberg in 1998<sup>2</sup> and the lipid flux theory are widely accepted. When Intralipid is administered intravenously, it creates a 'sink' which drives the toxic lipid soluble drugs from the tissues back into the newly created 'intravascular lipid compartment'. This may explain the ability of lipid emulsion to terminate convulsions.

Local anaesthetic drugs have been shown to inhibit enzymes responsible for fatty acid transfer into cellular mitochondria and this explains the 'lipid flux' theory. Tissues affected by bupivacaine-induced toxicity are those with the highest aerobic demand and least tolerance for hypoxia<sup>7</sup>. Administration of intralipid provides the mitochondria with sufficient fatty acids, restoring the heart's preferred energy source. Improved myocardial contractility has been demonstrated in an isolated rat heart model with lipid levels far lower to support a lipid sink effect<sup>8</sup>. The lipid flux theory may also explain why resuscitation is so rapid following lipid emulsion.

Another mechanism proposed is direct activation of voltage-gated calcium channels within the myocardium, increasing intracellular calcium levels leading to positive inotropic effect.

Based on the above mechanisms of action, Intralipid has been used in the management of toxicity from non local anaesthetic lipophilic drugs.

### **Indications**

1. Treatment of local anaesthetic toxicity
2. Treatment of lipophilic non local anaesthetic drug overdoses

### **Local Anaesthetics**

Local anaesthetics are drugs that cause a local reversible blockage of transmission of nerve impulses without affecting consciousness. The mechanism involves blockage of voltage-gated sodium channels within the neuron cell membrane. They are broadly classified into amino amide (Lidocaine, Bupivacaine, Ropivacaine, and Prilocaine) and amino esters (cocaine, procaine, and amethocaine). The commonly used local anaesthetic drugs are amethocaine, Lidocaine, Prilocaine, bupivacaine, and Ropivacaine.

The uses of local anaesthetics include topical analgesia, infiltration, peripheral nerve blockade, central nerve blockade, and as anti-arrhythmics (Lidocaine).

The action of each type of local anaesthetic is dependent on its lipid solubility, protein binding, vasodilating effects, added adjuvant and proportion of un-ionised drug at physiological pH.

The absorption of local anaesthetics from different sites is, from highest to lowest: endotracheal > intercostal > caudal > epidural > plexus blocks > sciatic/femoral > subcutaneous infiltration.

The rank order of local anaesthetic drugs toxicity is as follows (low to high): Prilocaine < Lidocaine < Ropivacaine < Levo-bupivacaine < Bupivacaine.

The metabolism of amide and ester local anaesthetics differs. Esters, with the exception of cocaine (hydrolysed in the liver) are rapidly metabolised by plasma esterase to inactive metabolites hence a shorter half life. Amides have a much slower metabolism by liver amidases and are therefore prone to accumulation during infusion or with hepatic dysfunction.

See Figure 2 for other properties of commonly used local anaesthetics:

**Figure 2<sup>9</sup>**

Local Anaesthetic	Dose maximum (with adrenaline)	Duration (hrs)	Potency	Onset of action	Protein binding (%)	pKa
Lidocaine	3(7) mg/kg	1	Medium	fast	65	7.9
Prilocaine	6(9) mg/kg	1.5	Medium	fast	55	7.9
Bupivacaine	2(2) mg/kg	2-4	High	slow	95	8.1
Ropivacaine	2(2) mg/kg	2-4	High	slow	95	8.1

## Local anaesthetics systemic toxicity (LAST)

The systemic toxicity from local anesthetic overdose was first described by Mayer in a 1928 report of 40 fatalities related to local anesthesia. In a 1979 seminal editorial, George Albright highlighted the risk from modern lipophilic local anaesthetics. Prior to the use of Intralipid, cardiopulmonary bypass was the only method shown effective in treating refractory cardiac arrest from local anaesthetic overdose<sup>10</sup>.

Local anaesthetics toxicity may occur due to<sup>11</sup>

- Accidental intravascular or intra-theal injection
- Relative over dosage of drug used
- Rapid systemic absorption from the injected site.

Local anaesthetic agents are thought to cause cardiotoxicity through

- ion channel blockade
- myocardial depression
- vasodilatation
- inhibition of mitochondrial oxidative metabolism

Local anaesthetic agents are thought to cause central nervous system (CNS) toxicity through

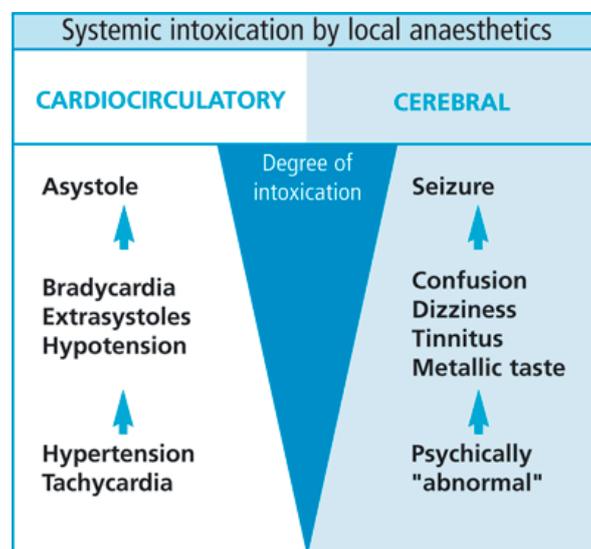
- Blockade of inhibitory pathways producing the initial excitation
- Excitatory activity leading to convulsions
- Inhibition of excitatory pathways leading to a generalised state of CNS depression

Local anaesthetic systemic toxicity may occur some time after an initial injection.

Signs of severe toxicity include:

- Sudden alteration in mental status, severe agitation, loss of consciousness, with or without tonic-clonic convulsions.
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular arrhythmias

See **Figure 3<sup>12</sup>**



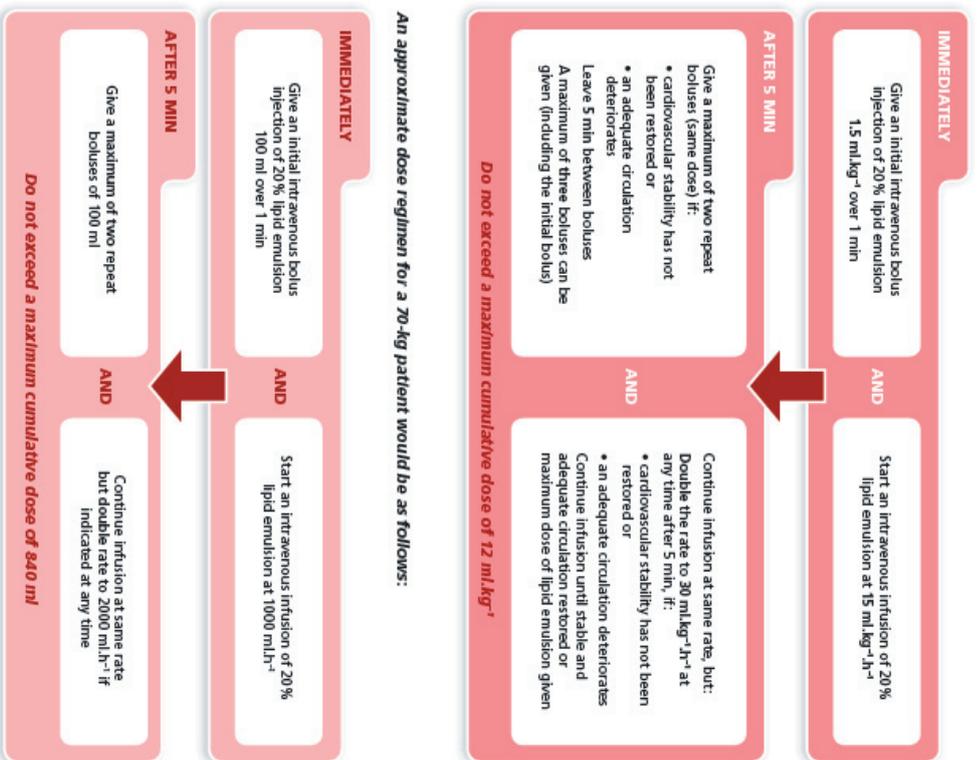
## Management of LAST

In 2010 the AAGBI issued revised guidelines on the use of Intralipid in local anaesthetics toxicity<sup>13</sup>. In the event of a cardiac arrest standard resuscitation protocols must be followed in addition to the use of Intralipid. See figure 4 overleaf.

Figure 4.

 <b>AAGBI Safety Guideline</b> Management of Severe Local Anaesthetic Toxicity	
<b>1</b>	<b>Recognition</b>  <b>Signs of severe toxicity:</b> <ul style="list-style-type: none"> <li>Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions</li> <li>Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur</li> <li>Local anaesthetic (LA) toxicity may occur some time after an initial injection</li> </ul>
<b>2</b>	<b>Immediate management</b> <ul style="list-style-type: none"> <li>Stop injecting the LA</li> <li>Call for help</li> <li>Maintain the airway and, if necessary, secure it with a tracheal tube</li> <li>Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)</li> <li>Confirm or establish intravenous access</li> <li>Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses</li> <li>Assess cardiovascular status throughout</li> <li>Consider drawing blood for analysis, but do not delay definitive treatment to do this</li> </ul>
<b>3</b>	<b>Treatment</b>  <b>IN CIRCULATORY ARREST</b> <ul style="list-style-type: none"> <li>Start cardiopulmonary resuscitation (CPR) using standard protocols</li> <li>Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory to treatment</li> <li>Consider the use of cardiopulmonary bypass if available</li> </ul>
	<b>WITHOUT CIRCULATORY ARREST</b> <ul style="list-style-type: none"> <li>Use conventional therapies to treat:                             <ul style="list-style-type: none"> <li>hypotension,</li> <li>bradycardia,</li> <li>tachyarrhythmia</li> </ul> </li> </ul>
<b>4</b>	<b>GIVE INTRAVENOUS LIPID EMULSION</b> (following the regimen overleaf) <ul style="list-style-type: none"> <li>Continue CPR throughout treatment with lipid emulsion</li> <li>Recovery from LA-induced cardiac arrest may take &gt;1 h</li> <li>Propofol is not a suitable substitute for lipid emulsion</li> <li>Lidocaine should not be used as an anti-arrhythmic therapy</li> </ul>
	<b>CONSIDER INTRAVENOUS LIPID EMULSION</b> (following the regimen overleaf) <ul style="list-style-type: none"> <li>Propofol is not a suitable substitute for lipid emulsion</li> <li>Lidocaine should not be used as an anti-arrhythmic therapy</li> </ul>
<b>4</b>	<b>Follow-up</b> <ul style="list-style-type: none"> <li>Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved</li> <li>Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days</li> <li>Report cases as follows:                             <ul style="list-style-type: none"> <li>In the United Kingdom: to the National Patient Safety Agency (via <a href="http://www.npsa.nhs.uk">www.npsa.nhs.uk</a>)</li> <li>In the Republic of Ireland: to the Irish Medicines Board (via <a href="http://www.imrb.ie">www.imrb.ie</a>)</li> </ul> </li> <li>If lipid has been given, please also report its use to the international registry at <a href="http://www.lipidregistry.org">www.lipidregistry.org</a>. Details may also be posted at <a href="http://www.lipidrescue.org">www.lipidrescue.org</a></li> </ul>

Your nearest bag of Lipid Emulsion is kept.....  
 This guideline is not a standard of medical care. The ultimate judgement with regard to particular clinical procedure or treatment plan must be made by the clinician in the light of the clinical data presented and the diagnostic and treatment options available.  
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This AAGBI safety guideline was produced by a Working Party that comprised: Grant Coak, Will Harrop-Griffiths (Chair), Mervyn Harvey, Tim Meek, John Picaud, Tim Short and Guy Wanberg. This safety guideline is endorsed by the Australian and New Zealand College of Anaesthetists (ANZCA).

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## Non-local anaesthetic toxicity

There are few case reports on the potential benefit of Intralipid in cardiac and CNS toxicity secondary to lipophilic non local anaesthetic drugs.

In animal models, intravenous lipid emulsion resulted in successful reversal of toxicity associated with Tricyclic antidepressants, verapamil, propranolol, and thiopentone. Intralipid use in human cases has resulted in successful resuscitation from combined bupropion/lamotrigine induced cardiac arrest, reversal of sertraline/quetiapine- induced coma, and reversal of verapamil and beta blocker induced shock<sup>14</sup>.

Other drugs overdoses successfully treated with Intralipid according to case reports are:

- Calcium channel blockers (verapamil<sup>15</sup>, nifedipine)
- Beta blockers (propranolol)<sup>16</sup>,
- Tricyclic antidepressants<sup>17</sup>
- Other psychotropic drugs (bupropion, lamotrigine<sup>18</sup> , quetiapine, sertraline<sup>19</sup> , haloperidol<sup>20</sup>
- Cocaine<sup>21</sup>
- Parasiticides, herbicides

The doses of Intralipid administered for non-local anaesthetic drug toxicity are similar to the ones suggested by the AAGBI guidelines<sup>13</sup>.

**Toxbase** recommends the use of lipid emulsion if cardiotoxicity is unresponsive to standard resuscitation measures. Tricyclic antidepressants, beta blockers, calcium channel blockers and carbamazepine are some of the drugs in which Toxbase recommends the use of Intralipid in the management of their toxicity. Toxbase acknowledges that the evidence for use of Intralipid is limited, and they encourage clinicians to report cases managed with Intralipid.

In adults and children the following regime is recommended:

1.5 mL/kg of 20% Intralipid as an intravenous bolus followed by 0.25 – 0.5 mL/kg/min for 30 - 60 minutes to an initial maximum of 500 mL.

The bolus could be repeated 1-2 times for persistent cardiovascular collapse or asystole. The infusion rate should be titrated against clinical response<sup>22</sup>.

## Risk of Intralipid treatment

It is worth noting that the information given here by the manufacturers is intended for Intralipid use in parenteral nutrition. Some of the risks may still apply to the short term use of Intralipid as in the management of drug toxicity.

Intralipid should be given with caution in conditions of impaired lipid metabolism such as renal insufficiency, uncompensated diabetes mellitus, pancreatitis, certain forms of liver insufficiency, hypothyroidism (if hypertriglyceridemic), metabolic disorders and sepsis. Fat embolism has been reported in a few cases when the recommended infusion rate has been exceeded in these patients.

This medicinal product contains soya-bean oil and egg phospholipids, which may rarely cause allergic reactions.

Animal reproduction studies have not been carried out with Intralipid but there are published reports of its successful and safe administration during pregnancy.

## Undesirable effects

In rare instances, initial administration of Intralipid has produced a rise in temperature, and less frequently shivering, chills and nausea or vomiting (incidence < 1%). Infusion of Intralipid should be discontinued in such cases. Other adverse event reports are extremely rare, occurring in less than one in one

million infusions. Hypersensitivity reactions, haemolysis, abdominal pain, priapism, headache and circulatory effects (hyper/hypotension), have been reported occurring immediately or soon after commencing Intralipid infusion.

Increased levels of transaminases, alkaline phosphatase and bilirubin have been observed in patients receiving intravenous nutrition, with or without Intralipid. If the dosage is reduced, values usually return to normal. Cholestasis has also been reported. Thrombocytopenia has been reported in association with prolonged treatment with Intralipid in infants.

Overdose leading to fat overload syndrome may occur – this is characterised by hyperlipidaemia, fever, fat infiltration, organ dysfunction and coma. All symptoms are usually reversible if the infusion is discontinued<sup>6</sup>. Despite an extensive list of possible risks, lipid emulsion appears well tolerated in clinical practice<sup>23</sup>.

Intralipid may interfere with certain laboratory measurements (bilirubin, lactate dehydrogenase, oxygen saturation, Hb etc) if blood is sampled before fat is adequately cleared from the blood stream. Fat is cleared after a fat free interval of four to six hours in most patients.

It is advisable to take all blood tests before administration of Intralipid and also inform the laboratory if blood tests are requested after giving Intralipid. Reports of difficulties in maintaining Continuous Renal Replacement Therapy (CRRT) following administration of lipid emulsion have been reported in the literature, presumably as a result of lipid molecules clogging the dialysis filter<sup>24</sup>.

In summary, despite possible adverse effects, lipid emulsion appears to have an evolving role in the management of patients with severe, life-threatening overdose of lipid soluble compounds.

## Local organisation

In most hospital in the UK, Intralipid is available in operating theatres. Local anaesthetic is however used in many other areas of the hospital such as the Emergency Department and Radiology.

It is of paramount importance that clinicians in these areas are aware of the existence of intravenous lipid emulsion, its indications and how to administer it.

Resuscitation teams and clinicians who administer local anaesthetics should be aware of the location of these drugs, so they can be accessed in an emergency.

The cost of maintaining Intralipid rescue kits in several locations is negligible when compared with patient safety implications. It has been suggested that Intralipid nearing expiry date may be returned to pharmacy for use as parenteral nutrition and replaced with new stock<sup>23</sup>.

The decision to use Intralipid in refractory non-local anaesthetic drug toxicity should be made on an individual case basis, as there are no guidelines in place and the evidence is based on animal studies and case reports.

The UK departments of health and the Health Protection Agency have recommended Toxbase as the first line source of poisons information for healthcare professionals within the NHS. Toxbase and the National Poisons Information Service should be consulted whenever in doubt about patient management.

## References

1. Intralipid from Wikipedia, <http://en.wikipedia.org/wiki/Intralipid> (accessed 01 November 2011)
2. Weinberg GL, VadeBoncouer T, Ramaraju GA, et al. Pre-treatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology*. 1998; 88(4):1071-5.
3. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006; 105: 217-8
4. Groban L, Butterworth J. Lipid reversal of bupivacaine toxicity: has the silver bullet been identified? *Reg Anesth Pain Med* 2003; 28: 167–9
5. Association of Anaesthetists of Great Britain and Ireland. <http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf>
6. UK Summary of Product Characteristics, Intralipid 20%, Fresenius Kabi Limited. (accessed 11/01/2012).
7. Lipid Rescue.org. <http://www.lipidrescue.org/> (accessed 01 November 2011)
8. Stehr SN, Pexa A, Hannack S, Heintz A, Heller AR, Deussen A, et al. The effects of lipid infusion on myocardial function and bioenergetics in L-bupivacaine toxicity in the isolated rat heart. *Anesth Analg* 2007; 104:186–92
9. Figure 2 adapted from Anaesthesia UK website Pharmacokinetics and toxicity local anaesthetics. <http://www.frca.co.uk/Search.aspx>. Created 19/07/2009. (Accessed 01/11/2011).
10. Weinberg GL. Lipid infusion therapy: translation to clinical practice *Anesth Analg*. 2008 May; 106(5):1340-42,
11. Miller's Anaesthesia, 7<sup>th</sup> edition, RD Miller et al, Churchill Livingstone
12. <http://www.nerveblocks.net> (accessed 10 October 2010)
13. Associations of Anaesthetists of Great Britain and Ireland. Guidelines for the Management of Severe Local Anaesthetic Toxicity. [http://www.aagbi.org/sites/default/files/la\\_toxicity\\_notes\\_2010\\_0.pdf](http://www.aagbi.org/sites/default/files/la_toxicity_notes_2010_0.pdf) [http://www.aagbi.org/sites/default/files/la\\_toxicity\\_2010\\_0.pdf](http://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf)
14. Cave G, Harvey M. Intravenous lipid emulsion as antidote beyond local anaesthetic toxicity: a systematic review. *Academic Emergency Medicine* 2009; 16(9): 815-24
15. Liang CW, Diamond SJ, Hagg DS. Lipid rescue of massive verapamil overdose: a case report. *J Med Case Reports* 2011; 5(1): 399
16. Jovic-Stosic J, Gligic B, Putic V, et al. Severe propranolol and ethanol overdose with wide complex tachycardia treated with intravenous lipid emulsion: a case report. *Clin Toxicol (Phila)* 2011; 49(5): 426-30
17. Hendon D, Menahga, Sandilands EA, Scullion D. Tricyclic Antidepressant Overdose in a Toddler Treated With Intravenous Lipid Emulsion *Paediatrics*. 2011 Dec; 128(6):e1628-32. Epub 2011 Nov 7
18. Sirianni AJ, Osterhoudt KC, Calello DP, et al. Use of lipid emulsion in resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Annals of Emergency Medicine* 2008; 51: 412-5
19. Finn SD, Uncles DR, Willers J, et al. Early treatment of a quetiapine and sertraline overdose with Intralipid. *Anaesthesia* 2011; 66(11):191-4
20. Weinberg G, Di Gregorio G, Hiller D, et al. Reversal of haloperidol- induced cardiac arrest by using lipid emulsion. *Annals of internal medicine* 2009; 150; 737-8
21. Jakkala-Saibaba R, Morgan P, Morton GL. Treatment of cocaine overdose with lipid emulsion. *Anaesthesia* 2011; 66(11): 1365-2044
22. Toxbase. <http://www.toxbase.org/> (accessed 10/01/2012).
23. Brull SJ. Lipid emulsion for the treatment of local anaesthetic toxicity: Patient safety implications. *Anaesthesia Anal* 2008; 106: 1337-1339
24. Karen Orr, Ronald Bailie. The use of Intralipid in the management of overdose: a case report. *JICS* volume 11 2010; 4: 268-69