BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2016, **119**, 345–348 Doi: 10.1111/bcpt.12607

Annotations & Reflections

Lipid Rescue – Efficacy and Safety Still Unproven

Jonas Höjer[1], Dag Jacobsen[2], Pertti J. Neuvonen[3] and Per H. Rosenberg[4]

[1]Swedish Poisons Information Center, Karolinska Institute, Stockholm, Sweden, [2]Department of Acute Medicine, Oslo University Hospital, Oslo, Norway, [3]Department of Clinical Pharmacology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland and [4]Department of Anaesthesiology and Intensive Care Medicine, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

(Received 19 February 2016; Accepted 8 April 2016)

Intralipid®, the soya bean oil-based nutritional lipid emulsion for intravenous administration, has maintained a remarkably safe record for more than 50 years. In conventional use, its rare adverse effects consist of pancreatitis, hepatic failure, dyspnoea and anaphylaxis, and these are usually due to overdose or too rapid infusion rate [1,2]. Intralipid® and other similar stable lipid emulsions have also pharmaceutical application as vehicles for various drugs such as diazepam, etomidate and propofol.

The idea of a possible antidotal effect of intravenous lipid emulsion on the action of lipophilic drugs was presented already in 1962 by Russell and Westfall who showed that barbiturate anaesthesias in rats were shorter when lipid emulsion was administered [3]. In 1998, Weinberg and colleagues reported that bupivacaine toxicity was reduced following pretreatment or resuscitation with intravenous lipid emulsion in rats [4]. The first patient with local anaesthetic systemic toxicity (LAST) treated with lipid emulsion with alleged successful effect was reported in 2006 [5] and the first patient treated because of an oral overdose of lipophilic drugs in 2008 [6]. Since these publications, the use of lipid emulsion as an antidote (lipid rescue) has increased rapidly worldwide. Starting in Great Britain in 2007 [7], anaesthesia associations and societies in several countries have launched guideline recommendations regarding the use of 20% lipid emulsion in LAST. The recommended dose would result in the administration of approximately 630 ml in 30 min. to a 70-kg patient, which deviates markedly from the established routine in nutritional therapy; that is, 'not more than 500 ml of 20% lipid emulsion should be infused on the first day of intravenous nutritional therapy' [1]. Among the medical toxicology societies, The American College of Medical Toxicology was first to publish a guidance statement regarding lipid resuscitation therapy in 2011 [8].

Author for correspondence: Per H. Rosenberg, Department of Anaesthesiology and Intensive Care Medicine, Biomedicum Helsinki 2C, Postbox 705, FI-00290 Helsinki, Finland (fax +358 9 4717409, e-mail per.rosenberg@helsinki.fi).

Perfused isolated rat heart [9–12], or some other variable experimental study design [13,14], has been used to demonstrate an antidotal effect of intravenous lipid emulsion on cardiotoxicity of local anaesthetics. Notably, many of the reports of such studies originate from one research group [4,9,13,14]. An increasing number of controlled animal studies have not, however, reported positive effects of this therapy in LAST [15–19]. Several experimental studies on the presumed beneficial effect of lipid rescue on the toxicity of other drugs than local anaesthetics have been negative or shown the opposite effect [20–22]. There is no well-designed controlled clinical study performed, wherefore the nearly two hundred published case reports and abstracts on the use of lipid rescue in LAST or oral poisonings represent the available human data [23,24]. When evaluating these cases, one should consider the importance of three well-known realities: firstly, the immense impact of publication bias; secondly, the fact that poisoning-induced signs and symptoms, in particular local anaesthetic-induced symptoms, often rapidly vanish spontaneously or after established therapeutic measures; thirdly, in a vast majority of the reported cases, also other resuscitative treatments have been given more or less simultaneously.

The authors of several review articles have analysed these cases and reported essentially the same conclusions, namely unclear mechanisms of action of lipid emulsion, lack of controlled human studies and not negligible adverse effects, and finally recommended that lipid rescue may be indicated in life-threatening lipophilic drug-induced symptoms when established therapy has failed [25–28]. In some of these reviews, experts have independently examined the cases according to an assessment form grading the probability for a causal connection between lipid rescue and improved symptoms. In most of the cases, the causal connection was assessed as uncertain, that is 'probable', 'possible' or 'unlikely' [27,28]. No correlation, not even a tendency towards correlation, was found between the ratings of the cases and the fat solubility of the respective toxins [28].

During the recent decade, a sliding of the indications for lipid rescue has occurred in clinical practice worldwide. Today, it is not uncommon that emergency physicians and intensivists give lipid rescue to patients who have overdosed a lipophilic drug orally, despite the lack of scientific support in this scenario. In fact, controlled experimental studies have shown worse outcome in orally poisoned animals given lipid rescue [29,30]. In some parts of the world, the enthusiasm for lipid rescue has reached a point when lipid emulsion is given as prophylaxis or as first-line therapy to patients with only moderate toxic symptoms after ingestion of modest toxic doses of lipid-soluble drugs [31]. If lipid rescue would be regarded as a primary therapy in patients with life-threatening symptoms, there is a risk that it steals valuable time from established potentially life-saving therapies, some of which lipid emulsion may counteract.

The initially proposed 'lipid sink theory' as an antidotal mechanism of action of lipid emulsion was readily assimilated. However, several reported cases of alleged successful outcome as a result of lipid rescue have involved only marginally lipophilic toxins. The recommended dose of lipid emulsion as antidote in human beings did not result in a significantly increased binding of bupivacaine or lidocaine to the lipid phase in plasma [32,33]. Other currently used local anaesthetics and most orally ingested toxins are less lipophilic than bupivacaine. Experiments in pigs, on the other hand, have shown that the strongly lipophilic anti-arrhythmic drug amiodarone (10^4 times more lipophilic than bupivacaine) is markedly bound to the lipoid plasma during lipid emulsion infusion [34]. Further, lipid emulsion was shown to increase the total plasma concentration of the lipophilic amitriptyline by reducing its distribution into highly perfused tissues and by facilitating its transfer back to plasma [35]; that is, the lipid emulsion seemed to serve more like a vehicle than a sink [36]. In this context, it is worth noticing that during the absorption phase of an oral overdose of lipophilic drugs such as amitriptyline or verapamil, lipid emulsion may facilitate absorption from the gastrointestinal tract and thereby aggravate the poisoning [29,30]. Other theories for antidotal mechanisms of lipid emulsion are metabolic mechanisms, for example proposed action on ionic channel permeability and on fatty acid utilization by the myocardium. The metabolic effects of lipid emulsion on the heart, which are suggested to aid in resuscitation from drug-induced severe cardiotoxicity, for example cardiac arrest, have been shown in experimental animals only with very high doses of lipid emulsion, 3 to 10 times those recommended in guidelines [14,37–40]. A direct translation of such doses into clinical therapy would make lipid rescue dangerous or impossible.

Adverse effects of lipid rescue have been largely ignored but increasingly reported. Valuable laboratory analyses, such as glucose, haematocrit, WBC, electrolytes and acid-base status, have not been possible to perform during several hours after lipid rescue because of laboratory interference caused by lipaemia [41–43]. Further, lipid rescue has been associated with the development of pancreatitis [31,42], severe pulmonary injury in the form of ARDS [42,43] and of deep venous thrombosis [44]. The use of extracorporeal membrane oxygenation after or during lipid rescue may be associated with fat deposition in the VA-ECMO circuits and increased blood clot formation [45]. It has been repeatedly reported that lipid rescue has rendered renal replacement therapy impossible because of filter collapse [43,46,47]. Moreover, Cole and colleagues reported two orally intoxicated patients who had cardiac arrest immediately after the lipid rescue bolus and finally had fatal outcome [48]. According to a very recent systematic review of clinical adverse events after lipid rescue [49], such events seemed to be proportional to the rate of lipid infusion as well as to the total dose.

Two systematic reviews from the American Academy of Clinical Toxicology's created workgroup Lipid Emulsion Therapy Workgroup were recently published [23,24]. The review on intravenous lipid emulsion for LAST concluded that lipid rescue appears to be effective in some cases of LAST, but there is currently no convincing evidence showing that it is more effective than vasopressors [23]. The review on lipid emulsion for non-local anaesthetics toxicity concluded that the quality of evidence for lipid rescue being an effective antidote in these scenarios remains low to very low [24]. There was no recommendation given regarding indications for lipid rescue in neither of the articles.

Considering the lack of evidence for positive effects of lipid rescue and its increasingly reported adverse effects, it is reasonable to be conservative in its use in clinical practice until better evidence on its efficacy and safety is available. In our opinion, this applies not only for oral poisonings but also for the patients with LAST. Adequate oxygenation, prompt institution of basic resuscitative measures and therapies with already validated specific antidotes in certain poisonings must not be delayed.

We conclude that it is high time to damp down the overenthusiasm for lipid rescue. If used uncritically, intravenous lipid emulsion may do more harm than good to the poisoned patients.

Declaration of Interest

The authors report no declaration of interest. The authors alone are responsible for the content and writing of the manuscript.

References

1 Food and Drug Administration. NDA 18-449/S039; NDA 17-643/S-072. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/018449s039,017643s072ltr.pdf (last accessed on 3 May, 2016).

2 Hippalgaonkar K, Majumdar S, Kansara V. Injectable lipid emulsions – advancements, opportunities and challenges. AAPS PharmSciTech 2010;**11**:1526–40.

3 Russell RL, Westfall BA. Alleviation of barbiturate depression. Anesth Analg 1962;**41**:582–5.

4 Weinberg GL, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Anesthesiology 1998;**88**:1071–5.

5 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**:217–18.

6 Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Walterhouse MR, Goodkin MB *et al.* Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. Ann Emerg Med 2008;**51**:412–15.

7 Picard J, Ward SC, Zumpe R, Meek T, Barlow J, Harrop-Griffiths W. Guidelines and the adoption of "lipid rescue" therapy for local anaesthetic toxicity. Anaesthesia 2009;**64**:122–5.

8 American College of Medical Toxicology. ACMT position statement: interim guidance for the use of lipid resuscitation therapy. J Med Toxicol 2011;**7**:81–2.

9 Weinberg GL, Ripper R, Murphy P, Edelman LB, Hoffman W, Strichartz G *et al.* Lipid infusion accelerates removal of bupivacaine and recovery from bupivacaine toxicity in the isolated rat heart. Reg Anesth Pain Med 2006;**31**:296–303.

10 Stehr SN, Ziegler JC, Pexa A, Oertel R, Koch T, Hubler M. The effect of lipid infusion on myocardial function and bioenergetics in l-bupivacaine toxicity in the isolated rat heart. Anesth Analg 2007;**104**:186–92.

11 Chen Y, Xia Y, Liu L, Shi T, Shi K, Wang Q *et al.* Lipid emulsion reverses bupivacaine-induced asystole in isolated rat hearts: concentration-response and time-response relationships. Anesthesiology 2010;**113**:1320–5.

12 Aumeier C, Kasdorf B, Gruber M, Busse H, Wiese CH, Zink W *et al.* Lipid emulsion pretreatment has different effects on mepivacaine and bupivacaine toxicity in an isolated rat heart model. Br J Anaesth 2014;**112**:735–41.

13 Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med 2003;**28**:198–202.

14 Fettiplace MR, Akpa BS, Ripper R, Zider B, Lang J, Rubinstein I *et al.* Resuscitation with lipid emulsion. Dose-dependent recovery from cardiac pharmacotoxicity requires a cardiotonic effect. Anesthesiology 2014;**120**:915–25.

15 Hicks SD, Salcido DD, Logue ES, Suffoletto BP, Empey PE, Poloyac SM *et al.* Lipid emulsion combined with epinephrine and vasopressin does not improve survival in a swine model of bupivacaine-induced cardiac arrest. Anesthesiology 2009;**111**:138–46.

16 Mauch J. Martin Jurado O, Spielmann N, Bettschart-Wolfensberger R, Weiss M. Comparison of epinephrine vs lipid rescue to treat severe local anesthetic toxicity - an experimental study in piglets. Paediatr Anaesth 2011;**21**:1103–8.

17 Litonius ES, Niiya T, Neuvonen PJ, Rosenberg PH. Intravenous lipid emulsion only minimally influences bupivacaine and mepivacaine distribution in plasma and does not enhance recovery from intoxication in pigs. Anesth Analg 2012;**114**:901–6.

18 Heinonen JA, Skrifvars MB, Haasio J, Rosenberg PH, Backman JT, Litonius E. Intravenous lipid emulsion for levobupivacaine intoxication in acidotic and hypoxaemic pigs. Anaesth Intensive Care 2016;**44**:270–7.

19 Buckenmeier CC III, Capacchione J, Mielke AR, Bina S, Shields C, Kwon KH *et al.* The effect of lipid emulsion on postmortem ropivacaine concentrations in swine: endeavoring to comprehend a soldier's death. Anesth Analg 2012;**114**:894–900.

20 Litonius E, Niiya T, Neuvonen PJ, Rosenberg PH. No antidotal effect of intravenous lipid emulsion in experimental amitriptyline intoxication despite significant entrapment of amitriptyline. Basic Clin Pharmacol Toxicol 2012;**110**:378–83.

21 Cave G, Harvey M, Quinn P, Heys D. Hypertonic sodium bicarbonate versus intravenous lipid emulsion in a rabbit model of intravenous flecainide toxicity: no difference, no sink. Clin Toxicol (Phila) 2012;**51**:394–7.

22 Varney SM, Bebarta VS, Vargas TE, Boudreau S, Castaneda M. Intravenous lipid emulsion therapy does not improve hypotension compared to sodium bicarbonate for tricyclic antidepressant toxicity: a randomized, controlled pilot study in a swine model. Acad Emerg Med 2014;**21**:1212–19.

23 Hoegberg LCG, Bania TC, Lavergne V, Bailey B, Turgeon AF, Thomas SHL *et al.* Systematic review of the effect of intravenous lipid emulsion therapy for local anesthetic toxicity. Clin Toxicol (Phila) 2016;**54**:167–93.

24 Levine M, Hoffman RS, Lavergne V, Stork CM, Graudins A, Chuang R *et al.* Systematic review of the effect of intravenous lipid emulsion therapy for non-local anesthetics toxicity. Clin Toxicol (Phila) 2016;**54**:194–221.

25 Cao D, Heard K, Foran M, Koyfman A. Intravenous lipid emulsion in the emergency department: a systematic review of recent literature. J Emerg Med 2015;**48**:387–97.

26 Jamaty C, Bailey B, Larocque A, Notabaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila) 2010;**48**:1–27.

27 Cave G, Harvey MG, Graudins A. Intravenous lipid emulsion as antidote: a summary of published human experience. Emerg Med Australas 2011;**23**:123–41.

28 Forsberg M, Forsberg S, Höjer J. Inget stöd för att lipidterapi är en effektiv antidot vid akut förgiftning [No support for lipid rescue being an effective antidote – a systematic review and analysis of 114 cases]. Läkartidningen 2015;**112**:1723–6.

29 Perichon D, Turfus S, Gerostamoulos D, Graudins A. An assessment of the *in vivo* effects of intravenous lipid emulsion on blood drug concentration and haemodynamics following oro-gastric amitriptyline overdose. Clin Toxicol (Phila) 2013;**51**:208–15.

30 Perichon D, Turfus S, Graudins A. Intravenous lipid emulsion does not improve hemodynamics or survival in a rodent model of oral verapamil poisoning. Clin Toxicol (Phila) 2013;**51**:277.

31 Cevik SE, Tasyurek T, Guneysel O. Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. Am J Emerg Med 2014;**32**:1103–8.

32 Litonius E, Tarkkila P, Neuvonen PJ, Rosenberg PH. Effect of intravenous lipid emulsion on bupivacaine plasma concentrations in humans. Anaesthesia 2012;**67**:600–5.

33 Heinonen JA, Litonius E, Salmi T, Haasio J, Tarkkila P, Backman JT *et al.* Intravenous lipid emulsion given to volunteers does not affect symptoms of lidocaine brain toxicity. Basic Clin Pharmacol Toxicol 2015;**116**:378–83.

34 Niiya T, Litonius E, Petäjä L, Neuvonen PJ, Rosenberg PH. Intravenous lipid emulsion sequesters amiodarone in plasma and eliminates its hypotensive action in pigs. Ann Emerg Med 2010;**56**:402–8.

35 Heinonen JA, Litonius E, Backman JT, Neuvonen PJ, Rosenberg PH. Intravenous lipid emulsion entraps amitriptyline into plasma and can lower its brain concentration – an experimental intoxication study in pigs. Basic Clin Pharmacol Toxicol 2013;**113**:193–200.

36 Picard J, Meek T. Lipid emulsion for intoxication by local anaesthetic: sunken sink? Anaesthesia 2016. doi: 10.1111/anae.13395

37 Teebutt S, Harvey M, Nicholson T, Cave G. Intralipid prolongs survival in a rat model of verapamil toxicity. Acad Emerg Med 2006;**13**:134–9.

38 Di Gregorio G, Schwartz D, Ripper R, Kelly K, Feinstein DL, Minshall RD *et al.* Lipid emulsion is superior to vasopressin in a rodent model of resuscitation from toxin-induced cardiac arrest. Crit Care Med 2009;**37**:993–9.

39 Fettiplace MR, Pichurko A, Ripper R, Lin B, Kowal K, Lis KK *et al.* Cardiac depression induced by cocaine or cocaethylene is alleviated by lipid emulsion more effectively than by

sulfobutylether-β-cyclodextrin. Acad Emerg Med 2015;**22**:508–17.
40 Kang C, Kim DH, Kim SC, Lee SH, Jeong JH, Kang TS *et al.* The effects of intravenous lipid emulsion on prolongation of survival in a rat model of calcium channel blocker toxicity. Clin Toxicol (Phila) 2015;**53**:540–4.
41 Grunbaum AM, Gilfix BM, Hoffman RS, Lavergne V, Morris M, Miller-Nesbitt A *et al.* Review of the effect of intravenous lipid emulsion on laboratory analyses. Clin Toxicol (Phila) 2016;**54**:92–102.
42 Levine M, Skolnik AB, Ruha AM, Bosak A, Menke N, Pizon AF. Complications following antidotal use of intravenous lipid emulsion therapy. J Med Toxicol 2014;**10**:10–14.
43 Martin C, Gonzalez H, Ruiz S, Ribes D, Franchitto N, Minville V. Acute respiratory distress syndrome following verapamil overdose treated with intravenous lipid emulsion: a rare life-threatening complication. Ann Fr Anesth Reanim 2014;**33**:101–2.
44 Schwarz ES, Arroyo-Plasencia AM, Mullins ME. Other complications following lipid emulsion therapy. J Med Toxicol 2014;**10**:247–8.
45 Lee HMD, Archer JRH, Dargan PI, Wood DM. What are the adverse effects associated with the combination use of intravenous lipid emulsion and extracorporeal membrane oxygenation in the poisoned patient? Clin Toxicol (Phila) 2015;**53**:145–50.
46 Rodrigues B, Wilhelm A, Kokko KE. Lipid emulsion use precluding renal replacement therapy. J Emerg Med 2014;**47**:635–7.
47 Jeong J. Continuous renal replacement therapy circuit failure after antidote administration. Clin Toxicol (Phila) 2014;**52**:1296–7.
48 Cole JB, Stellpflug SJ, Engebretsen KM. Asystole immediately following intravenous fat emulsion for overdose. J Med Toxicol 2014;**10**:307–10.
49 Hayes BD, Gosselin S, Calello DP, Nacca N, Rollins CJ, Abourbih D *et al.* Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration. Clin Toxicol (Phila) 2016;**54**:365–404.