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USE OF INTRAVENOUS FAT EMULSION IN THE EMERGENCY DEPARTMENT FOR THE CRITICALLY ILL POISONED PATIENT

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Abstract—Background: Multiple case reports of using intravenous fat emulsion (IFE) as an antidote for human poisoning from various xenobiotics have been published over the last decade. Given the rapidly evolving field, emergency physicians may be uncertain about the indications, timing, and dose for IFE treatment. Methods: A PubMed literature search was conducted from January 1996 to November 2015 and limited to human studies written in English and articles with relevant keywords. Guideline statements and nonsystematic reviews were excluded. Studies identified then underwent a structured review of their results. Results: There were 986 papers fulfilling the search criteria screened, and 85 appropriate articles were rigorously reviewed in detail. Recommendations were given on indications, timing, and dose of IFE. Most of these were based on case reports and anecdotal experience. Discussion: In critically ill patients with refractory shock or cardiac arrest after a suspected overdose of local anesthetics or selected xenobiotics, IFE may be considered as a potentially beneficial adjunctive treatment. Despite an abundance of reports on the use of IFE on xenobiotics poisoning, the quality of evidence is suboptimal and fraught with reporting bias. Conclusions: IFE may be an effective antidote in poisonings from various xenobiotics. However, further research is needed to determine its optimal circumstances, timing, and dose of use. © 2016 Elsevier Inc.

Keywords—intravenous fat emulsion; poisoned patient; review

INTRODUCTION

The successful use of intravenous fat emulsion (IFE) for the adverse effects associated with local anesthetics has led to its consideration as an antidote for multiple xenobiotics/substances (1–6). Similar to most toxicology research, the evidence is almost completely reliant on animal experiments and human case reports. In addition to lack of definitive efficacy, there is the question of safety. Fat emboli, acute lung injury, cardiac arrest, and deep venous thrombosis have been associated with IFE use. Hypersensitivity, lipemia, pancreatitis, interference with standard medication therapies, and analytical interference with certain laboratory assays are all concerns of unproven clinical significance (7–11).

Our goal is to supply emergency physicians with a practical guideline for the use of IFE in critically poisoned patients, and provide evidence supporting its therapeutic efficacy. Specific focus was given to xenobiotics overdoses that may benefit from administration of IFE, timing of IFE administration, and recommended dose of IFE.

METHODS

A structured review of the medical literature using PubMed was performed and limited to studies published from January 1996 to November 2015. Inclusion criteria were all studies involving human subjects and written in the English language and containing the following keywords: “intravenous” AND [“fat emulsion” OR “lipid...
emulsion” OR “lipid” OR “intralipid”) AND [“resuscitation” OR “poisoning” OR “toxicity” OR “overdose” OR “antidote” OR “rescue”]. References of selected review articles were also screened for potential additional studies (1–6). The abstracts of the articles found in this search were assessed independently by two of the authors, to determine which papers should be pulled for more detailed review based on their suspected relevance to the clinical question. Studies included for the final detailed review were limited to randomized controlled trials, prospective trials, retrospective cohort trials, case series, and case reports in human subjects. General review articles and abstracts presented at conferences were not included for formal review. Cases documented on the Web forum http://www.lipidrescue.org were excluded as they were not peer-reviewed.

Each of the selected articles was subjected to detailed review by at least two of the authors. The level of the evidence was assigned a Grade of Evidence using the definitions as noted in Table 1 and were based on reference focus, specific research design, and methodology. Each of the selected articles was also subjected to detailed review and assigned a Quality Ranking based on a critical assessment with regard to quality of the design and methodology. This includes Design Consideration (e.g., focus, model structure, presence of controls) and Methodology Consideration (actual methodology utilized). The definitions of the Quality Ranking scores are included in Table 2.

Independent review of the articles as well as discussion and joint review by the authors was undertaken to answer the clinical questions. The references were sorted into three categories: supportive, neutral, and opposed. A table was constructed to assign the supportive references to the appropriate location using both the Grade of Evidence and Quality Ranking.

**Table 1. The Definitions of the Grades of Evidence of the Articles**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue</td>
</tr>
<tr>
<td>Grade B</td>
<td>Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue</td>
</tr>
<tr>
<td>Grade C</td>
<td>Prospective, controlled, nonrandomized, cohort studies</td>
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<tr>
<td>Grade D</td>
<td>Retrospective, nonrandomized, cohort or case-control studies</td>
</tr>
<tr>
<td>Grade E</td>
<td>Case series, animal/model scientific investigations, theoretical analyses, or case reports</td>
</tr>
<tr>
<td>Grade F</td>
<td>Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice</td>
</tr>
</tbody>
</table>

Finally, recommendations were made based on the review of the literature and assigned a level of recommendation that is defined in Table 3.

**RESULTS**

The PubMed search using the method outlined above resulted in 986 unique articles of human studies written in English. Two emergency physicians independently assessed the abstracts of the articles. A total of 85 articles were deemed appropriate to be included in this summary. These articles include: randomized controlled trials (n = 1), retrospective cohort or case-control studies (n = 4), case series/case reports (n = 79), and editorial/rational conjecture (n = 1).

** Recommendation 1 – For Which Substances are There Potential Benefits When IFE is Administered?**

Whereas the original animal studies and human case reports of IFE were on its use in local anesthetic overdose, IFE has since been shown to be effective in overdose of multiple xenobiotics. Recently a number of case reports have been published on its use in specific pediatric poisonings as well (12–23). Considering most of our knowledge of IFE in human poisonings came from cases reports, and the paucity of double-blinded placebo-controlled studies, limitations exist with regard to its definitive applicability to patients. It is uncertain what the optimal IFE treatment protocol is for all of these substances. There might also be unstudied xenobiotics, which could be effectively treated with IFE.

We focused on those xenobiotics with some published evidence for beneficial effects of IFE (12–87) As a result, we created two categories: 1 – Probable benefit and 2 – Possible benefit. Tables 4 and 5 list the supportive references along with the appropriate classifications.
using both Grade and Quality of Evidence. Additionally, there were seven neutral or opposed references for this clinical question (88–94).

Probable Benefit (12–19,24–45)

All local anesthetics including:
- Bupivacaine
- Mepivacaine
- Ropivacaine
- Levobupivacaine
- Prilocaine
- Lignocaine
- Lidocaine

Possible Benefit (20–23,46–87)

- Amitriptyline
- Amlodipine
- Atenolol
- Baclofen
- Bupropion
- Carbamazepine
- Carvedilol
- Chlorpromazine
- Clomipramine
- Cocaine
- Diltiazem
- Diphenhydramine
- Dosulepin
- Dothiepin
- Doxepin
- Endosulfan
- Felodipine
- Flecainide
- Glyphosate/Polyoxyethylene amine surfactant
- Haloperidol
- Hydroxychloroquine
- Imipramine
- Lamotrigine
- Metoprolol
- Nebivolol
- Nifedipine
- Olanzapine
- Phenobarbital
- Propafenone
- Propranolol
- Quetiapine
- Thiopental
- Venlafaxine
- Verapamil

Recommendation: IFE is probably beneficial in treatment of local anesthetic overdose. Consultation with a medical toxicologist is recommended prior to initiation of overdose treatment from other xenobiotics. Level of recommendation: Class B2.

Recommendation 2 – When Should IFE Be Administered?

The optimal timing of administration of IFE is unclear and has not been studied adequately. The American College of Medical Toxicology (ACMT) recommends that IFE be used for poisoned patients with hemodynamic or other instability not responding to standard resuscitation measures (97). This is consistent with the circumstances of most case reports (12–87). Reports of IFE given for mental status change only in overdosed patients noted little if any difference in outcome in

<table>
<thead>
<tr>
<th>Level of Recommendation</th>
<th>Criteria for Level of Recommendation</th>
<th>Mandatory Evidence</th>
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</thead>
<tbody>
<tr>
<td>Class A (Recommended with outstanding evidence)</td>
<td>- Acceptable&lt;br&gt;- Safe&lt;br&gt;- Useful&lt;br&gt;- Established/definitive</td>
<td>- Level A/B grade&lt;br&gt;- Outstanding quality&lt;br&gt;- Robust&lt;br&gt;- All positive</td>
</tr>
<tr>
<td>Class B (Acceptable &amp; appropriate with good evidence)</td>
<td>- Acceptable&lt;br&gt;- Safe&lt;br&gt;- Useful&lt;br&gt;- Not yet definitive&lt;br&gt;- Standard approach</td>
<td>- Level A/B grade lacking&lt;br&gt;- Adequate to Good quality&lt;br&gt;- Most evidence positive&lt;br&gt;- No evidence of harm&lt;br&gt;- Consistently positive</td>
</tr>
<tr>
<td>Class B 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class B 2</td>
<td>- Optional or alternative approach</td>
<td>- Lower grades of evidence&lt;br&gt;- Generally, but not consistently, positive</td>
</tr>
<tr>
<td>Class C (Not acceptable or not appropriate)</td>
<td>- Unacceptable&lt;br&gt;- Unsafe&lt;br&gt;- Not useful</td>
<td>- No positive evidence&lt;br&gt;- Evidence of harm</td>
</tr>
<tr>
<td>Class Indeterminate (Unknown)</td>
<td>- Minimal to no evidence</td>
<td>- Minimal to no evidence</td>
</tr>
<tr>
<td>Ref. #</td>
<td>Article Information</td>
<td>Grade</td>
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<tr>
<td>Drug levels included after IFE given</td>
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<td>Drug levels included after IFE given</td>
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<td></td>
</tr>
<tr>
<td>Drug levels included after IFE given</td>
<td></td>
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<tr>
<td>10 (32)</td>
<td>Whiteside J. Reversal of local anesthetic induced CNS toxicity with lipid emulsion. Anaesthesia 2008;63:202–4.</td>
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(Continued)
Table 4. Continued

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<thead>
<tr>
<th>Ref. #</th>
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<th>Grade</th>
<th>Quality</th>
<th>Design/Size</th>
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<tbody>
<tr>
<td>20 (38)</td>
<td>Gallagher C, Tan JM, Foster CG. Lipid rescue for bupivacaine toxicity during cardiovascular procedures. Heart Int 2010;5:e5</td>
<td>E</td>
<td>Poor</td>
<td>Case report (n = 1)</td>
</tr>
<tr>
<td>23 (39)</td>
<td>Varela H, Burns SM. Use of lipid emulsions for treatment of local anesthetic toxicity: a case report. AANA J 2010;78:359–64.</td>
<td>E</td>
<td>Poor</td>
<td>Case report (n = 1)</td>
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<tr>
<td>(Ref. #)</td>
<td>Article Information</td>
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<td>Quality</td>
<td>Design/Size</td>
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<tr>
<td>36 (50)</td>
<td>Engels PT, Davidow JS. Intravenous fat emulsion to reverse haemodynamic instability from intentional amitriptyline overdose. Resuscitation 2010;81:1037–9.</td>
<td>E</td>
<td>Poor</td>
<td>Case report (n = 1)</td>
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</table>

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<th>Grade</th>
<th>Quality</th>
<th>Design/Size</th>
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<tr>
<td>58 (23)</td>
<td>McAllister RK, Tuft CD, Colvin CS. Lipid 20% emulsion ameliorates the symptoms of olanzapine toxicity in a 4-year-old. Am J Emerg Med 2012:30:1012e1–2.</td>
<td>E</td>
<td>Poor</td>
<td>Case report (n = 1)</td>
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<table>
<thead>
<tr>
<th>(Ref.)</th>
<th>Article Information</th>
<th>Grade</th>
<th>Quality</th>
<th>Design/Size</th>
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(Continued)
some cases, but clinically significant improvement in others (70,73,89,94). Furthermore, IFE has not been directly compared with (and proven to be more effective than) standard seizure therapies such as benzodiazepines.

It is therefore reasonable to recommend that IFE be given in patients overdosed on local anesthetics who show signs of cardiovascular collapse or refractory shock. This should be done concomitantly with standard cardiopulmonary resuscitation according to the Advanced Cardiac Life Support protocol, inotropes and pressors administration. Similarly, IFE should be considered for overdose of other xenobiotics (see list under recommendation 1) in cases of cardiac arrest or refractory shock where standard resuscitation therapies have failed or would not be considered efficacious.

Recommendation: IFE is recommended in conjunction with standard resuscitation therapies in poisoned patients who are hemodynamically unstable. Level of recommendation: Class B2.

Table 4. Continued

<table>
<thead>
<tr>
<th>(Ref. #)</th>
<th>Article Information</th>
<th>Grade</th>
<th>Quality</th>
<th>Design/Size</th>
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<tr>
<td>78 (89)</td>
<td>Watt P, Malik D, Dyson L. Gift of the glob—is it foolproof? Anaesthesia 2009;64:1031–3.</td>
<td>E</td>
<td>Poor</td>
<td>Case series (n = 2)</td>
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<td>82 (93)</td>
<td>Bazerbachi F, Rank K, Chan A. Intravenous lipid rescue and ropivacaine systemic toxicity. J Anesth 2014;28:139.</td>
<td>E</td>
<td>Poor</td>
<td>Case report (n = 1)</td>
</tr>
</tbody>
</table>

IFE = intravenous fat emulsion.

Table 5. Evidence Rating (Article# Referenced in Table 4)

<table>
<thead>
<tr>
<th>Quality/Grade</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outstanding</td>
<td>59</td>
<td>55,68</td>
<td>43</td>
<td>76,83</td>
<td>5,6,9,22,24–26, 31,34,41,45, 48, 49,51,54,57,60, 65,67,70–73,79</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>45</td>
<td>33,37</td>
<td>78,87</td>
<td>31,34,41,45, 48, 49,51,54,57,60, 65,67,70–73,79</td>
<td></td>
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<tr>
<td>Adequate</td>
<td>1–4,7,8,10–21,23, 27–30,32,33, 35–40,42,44,46,47,50,52, 53,56,58,61–64, 66,69,74,75,77,78, 80–82,84</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Poor</td>
<td>85</td>
<td>55,68</td>
<td>43</td>
<td>76,83</td>
<td>5,6,9,22,24–26, 31,34,41,45, 48, 49,51,54,57,60, 65,67,70–73,79</td>
<td></td>
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<tr>
<td>Unsatisfactory</td>
<td></td>
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</table>
**Recommendation 3 – What Dose and Duration of IFE Should Be Used?**

Twenty percent IFE has been the most commonly studied formulation in poisonings, though other lipid formulations exist with varying concentrations. The ACMT recommends that 20% IFE be given as a 1.5-mL/kg bolus, which may be repeated in cases of asystole or pulseless electrical activity. This may be followed by an infusion of 0.25 mL/kg/min for up to 60 min. In case of re-emergence of hemodynamic instability after initial response, the bolus could be repeated or the infusion rate could be increased (97). The Association of Anaesthetists of Great Britain and Ireland guidelines recommends a similar regimen with a maximum dose of 12 mL/kg for local anesthetic toxicity (98).

These recommendations were derived from cases of local anesthetic poisoning, which tend to be short lived. In addition, the maximal duration of IFE infusion was not specified. The United States Food and Drug Administration recommends an upper limit of 12.5 mL/kg of 20% IFE over 24 h in adults, and 15 mL/kg over 24 h in pediatric patients, though this was established with the intention of IFE being used as a nutritional infusion rather than an antidote. In practice, when IFE was used for nonlocal anesthetic poisoning, infusion of up to 19 days, and total volume as high as 6200 mL (79 mL/kg body weight), over 5 h have been reported (84,95).

In a recent article, Fettiplace et al. recommended a maximum initial 20% IFE load of 2.25 mL/kg, followed by 0.025 mL/kg/min if needed, for no more than 6.5 hours, as a balance between benefits and potential adverse effects (96). This would ideally need to be validated by future clinical trials.

Recommendation: Twenty percent IFE can be given as a 1.5-mL/kg bolus in case of xenobiotics poisoning. Consider repeat dose(s) every 5 min until cardiovascular stability is achieved. This may be followed by an infusion of 0.025–0.25 mL/kg/min. Preferably, total 24 h dosing should be under 12.5 mL/kg. Level of recommendation: Class B2.

**DISCUSSION**

In this article, we have reviewed the current published literature and made recommendations of the indications, timing, and dose of IFE use in cases of xenobiotics poisoning. In critically ill patients with refractory shock or cardiac arrest after a suspected overdose of local anesthetic and other listed agents, IFE may be considered as a potentially beneficial adjunctive treatment. A bolus dose of 1.5 mL/kg seems reasonable, which may be repeated and followed by an infusion of 0.025–0.25 mL/kg/min if needed. Early consultation with a medical toxicologist should be considered to guide the exact course of therapy.

Reporting bias limits the definitive interpretation of the existing literature. In addition, human evidence is limited to mostly case reports that provide most of our current knowledge beyond animal studies regarding the efficacy of IFE. IFE deserves more rigorous human studies. International databases such as those of the Toxicology Investigators Consortium (ToxIC) show promise to provide more answers in the future (68).

**CONCLUSION**

In critically ill patients with a suspected overdose of local anesthetics, IFE should be considered as a potentially beneficial adjunctive treatment. For overdose of all other xenobiotics, consultation with a medical toxicologist may be warranted to determine risk vs. benefit. Studies with more rigorous designs are needed to elaborate on its optimal indications, timing, and dose.

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  caine induced cardiac arrest linked to recent simulation training. 
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  diovascular collapse after supraclavicular brachial plexus block. 
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