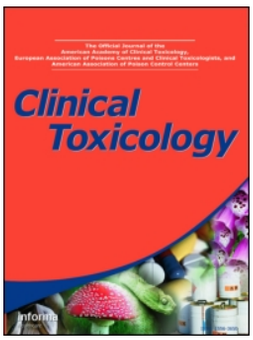

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: http://www.tandfonline.com/loi/ictx20

Advancing the science of antidotal use of lipid emulsion

Michael E. Mullins

To cite this article: Michael E. Mullins (2016) Advancing the science of antidotal use of lipid emulsion, Clinical Toxicology, 54:10, 897-898, DOI: 10.1080/15563650.2016.1216558

To link to this article: http://dx.doi.org/10.1080/15563650.2016.1216558

CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 10, 897–898
http://dx.doi.org/10.1080/15563650.2016.1216558

Taylor & Francis
Taylor & Francis Group

COMMENTARY

Advancing the science of antidotal use of lipid emulsion

Michael E. Mullins

Division of Emergency Medicine, Washington University School of Medicine, Saint Louis, MO, USA

Recent years have seen rapid growth in the number and variety of published cases of the antidotal use of intravenous lipid emulsion (ILE) in poisoned patients, usually with successful outcomes. However, publication bias generally favors reports of good outcomes with novel treatments. This bias leads to enthusiasm in which ILE may not fully deserve.

A 2010 systematic review by Jamaty et al. summarized the human case reports and animal trials of ILE for various poisonings.[1] The authors concluded that these data suggested likely benefit for local anesthetic toxicity and possible benefit for a few other cardiotoxic drugs. In 2011, the American College of Medical Toxicology published a position statement which mentioned "uncertainty of its beneficial effects in human poisonings" and gave suggestions on how to administer ILE without suggestion when to use it.[2] More recently, Lam et al. published a position paper for the American Academy of Emergency Medicine [3] and reached the same conclusions as Jamaty et al.

With this issue, we have the final installment of the work of the Lipid Emulsion Workgroup.[4] The workgroup comprised two dozen experts (representing the American Academy of Clinical Toxicology, the European Association of Poison Centres and Clinical Toxicologists, the Asia Pacific Association of Medical Toxicology, the American College of Medical Toxicology the American Association of Poison Control Centers, and the Canadian Association of Poison Control Centres) who convened to assess the evidence concerning four facets of antidotal use of ILE. After setting out the rigorous methodology for selecting and rationally appraising the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach,[5–7] sub-groups prepared in-depth reports regarding ILE for local anesthetic poisoning,[8] ILE for other acute poisonings,[9] laboratory interferences associated with ILE,[10] and adverse events associated with ILE.[11]

Local anesthetics share similar mechanism and clinical effects but differ in their lipophilicity. Their octanol/water partition coefficients, expressed as a logarithm of the ratio of concentrations (log D), vary from 1.26 for lidocaine to 4.21 for ropivacaine. Bupivacaine, which has the largest share of human and animal data, has a log D of 2.68 (suggesting that the concentration in the lipid phase is nearly 500 times the concentration in the aqueous phase. The effects of ILE in LA poisoning appear relatively consistent, although ILE may not be the silver bullet that never fails.[8] For other poisonings, the toxins and the outcomes vary more widely.[9]

If the lipid sink or facilitated redistribution explains the antidotal effect of lipid emulsion, then the log D should predict the likelihood of successful antidotal use of ILE for a given drug. However, some outlier cases appear to show success against a few water-soluble drugs, and others appear to show underwhelming results against very lipid-soluble drugs. Until stronger data emerge, future reports of the antidotal ILE should consistently report the log D for the toxin. However, at this time, we should move beyond case reports and testimonials to more rigorous investigations yielding higher quality evidence about clinical effectiveness of ILE.

The review of laboratory interferences with ILE should serve as a comprehensive guide to expected laboratory abnormalities associated with the antidotal use of ILE.[10] If ILE is truly life-saving, the temporary difficulty in interpreting certain test results should be a minor inconvenience to the treating physicians. A desirable therapy must be both effective and safe. The working group painstakingly catalogued the adverse events reported to occur with ILE in either nutritional or antidotal use.[11] With decades of widespread experience with ILE in total parenteral nutrition (TPN), this body of literature may foretell the adverse events possible with the antidotal use of ILE. However, the patients receiving TPN differ from acutely poisoned patients in several ways. TPN patients are sick for different reasons. Many of the adverse events occurred in premature infants whose care occurred years ago or in critically ill surgical patients. TPN patients generally receive longer courses of ILE. The interested reader should carefully compare one's patient to the TPN patients to draw conclusions about the potential risks of this still-new antidotal therapy.

In the final paper summarizing the recommendations of the Lipid Emulsion Workgroup, the working group carefully considered several specific questions for various toxins.[4] When should ILE be the first-line therapy? Is ILE the drug of choice in cardiac arrest or life-threatening toxicity? Should we ever use ILE in nonlife-threatening toxicity of specific drugs? The working group has carefully made recommendations only for toxins with a minimum of three case reports and then only when group consensus was clear. Many of their recommendations are neutral, and their few positive recommendations come with caveats and considerations. To

CONTACT Michael E. Mullins mullinsm@wustl.edu Division of Emergency Medicine, Washington University School of Medicine, Saint Louis, Missouri 63110, USA

This article was originally published with errors. This version has been amended. Please see Corrigendum (http://dx.doi.org/10.1080/15563650.2016.1230271).

paraphrase a quote often attributed to the astronomer Carl Sagan, the absence (or paucity) of evidence of effect of ILE for a particular drug is not evidence of absence.

Taken together, the work of the Lipid Emulsion Workgroup should temper the enthusiasm for ILE with the awareness that both good and bad effects may occur. The published evidence largely comprises case reports and small case series. Consequently, the majority of evidence is still of low quality. The commendable efforts of the working group should form the foundation for comparing and reporting future experiences with ILE with greater objectivity.

Disclosure statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this article.

ORCiD

Michael E. Mullins http://orcid.org/0000-0001-8605-0217

References

[1] Jamaty C, Bailey B, Larocque A, et al. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila). 2010;48:1–27.

[2] American College of Medical Toxicology. ACMT position statement: interim guidance for the use of lipid resuscitation therapy. J Med Toxicol. 2011;7:81–82.

[3] Lam SHF, Majlesi N, Vilke GM. Use of intravenous fat emulsion in the emergency department for the critically ill poisoned patient. J Emerg Med. 2016. [Epub ahead of print]. http://dx.doi.org/10.1016/j.jemermed.2016.02.008.

[4] Gosselin S, Hoegberg LCG, Hoffman RS, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol. Forthcoming 2016.

[5] Gosselin S, Morris M, Miller-Nesbitt A, et al. Methodology for AACT evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol. 2015;53:557–564.

[6] Guyatt GH, Oxman AD, Kunz R, et al. Incorporating considerations of resources use into grading recommendations. BMJ. 2008;336:1170–1173.

[7] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–926.

[8] Hoegberg LCG, Bania TC, Lavergne V, et al. Systematic review of the effect of intravenous lipid emulsion therapy for local anesthetic toxicity. Clin Toxicol. 2016;54:167–193.

[9] Levine M, Hoffman RS, Lavergne V, et al. Systematic review of the effect of intravenous lipid emulsion therapy for non-local anesthetics toxicity. Clin Toxicol. 2016;54:194–221.

[10] Grunbaum AM, Gilfix BM, Hoffman RS, et al. Review of the effect of intravenous lipid emulsion on laboratory analyses. Clin Toxicol (Phila). 2016;54:92–102.

[11] Hayes BD, Gosselin S, Calello DP, et al. Systematic review of adverse effect of intravenous lipid emulsion therapy. Clin Toxicol. 2016;54:365–404.