Lipid Rescue 911: Are Poison Centers Recommending Intravenous Fat Emulsion Therapy for Severe Poisoning?

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Abstract Intravenous fat emulsion (IFE) therapy is a novel treatment that has been used to reverse the acute toxicity of some xenobiotics with varied success. We sought to determine how US Poison Control Centers (PCCs) have incorporated IFE as a treatment strategy for poisoning. A closed-format multiple-choice survey instrument was developed, piloted, revised, and then sent electronically to every medical director of an accredited US PCC in March 2011. Addresses were obtained from the American Association of Poison Control Centers listserv, and participation was voluntary and remained anonymous. Data were analyzed using descriptive statistics. The majority of PCC medical directors completed the survey (45 out of 57; 79 %). Of the 45 respondents, all felt that IFE therapy played a role in the acute overdose setting. Most PCCs (30 out of 45; 67 %) have a protocol for IFE therapy. In a scenario with “cardiac arrest” due to a single xenobiotic, directors stated that their center would “always” or “often” recommend IFE after overdose of bupivacaine (43 out of 45; 96 %), verapamil (36 out of 45; 80 %), amitriptyline (31 out of 45; 69 %), or an

unknown xenobiotic (12 out of 45; 27 %). In a scenario with “shock” due to a single xenobiotic, directors stated that their PCC would “always” or “often” recommend IFE after overdose of bupivacaine (40 out of 45; 89 %), verapamil (28 out of 45; 62 %), amitriptyline (25 out of 45; 56 %), or an unknown xenobiotic (8 out of 45; 18 %). IFE therapy is being recommended by US PCCs; protocols and dosing regimens are nearly uniform. Most directors feel that IFE is safe but are more likely to recommend IFE in patients with cardiac arrest than in patients with severe hemodynamic compromise.

Keywords Intralipid · Intravenous fat emulsion · Lipid resuscitation therapy · Poison center · Antidote

Introduction

Intravenous fat emulsion (IFE) therapy is a novel treatment that is being used to reverse the acute toxicity of some xenobiotics with varied success. Weinberg et al. first demonstrated that pretreatment with IFE decreased bupivacaine-induced cardiotoxicity in a rat model [1]. Rosenblatt et al. published the first human case report of IFE use in bupivacaine-induced cardiac arrest, marking the transition from bench to bedside [2]. IFE has since been used successfully in numerous case reports for toxicity from a variety of xenobiotics including bupropion [3], verapamil [4, 5], quetiapine [6], venlafaxine [7], propranolol [8], and diltiazem [9]. IFE has been used with varied success in several animal models as well [10]. Medical toxicologists across the USA are adopting IFE as a treatment strategy primarily based on case reports and animal data in the absence of high-quality human studies where dose, timing, and other variables can be controlled.

Despite use by many medical toxicologists, to date, there remains no standard on using IFE in poisonings. In late 2010, the American College of Medical Toxicology (ACMT) issued only an “interim” position statement on this

Data were previously presented at the 2011 North American Congress of Clinical Toxicology (NACCT) Fellow-In-Training Platform session.

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therapy: “Given the uncertainty of its beneficial effect in human poisonings, it is the opinion of the American College of Medical Toxicology that there are no standard of care requirements to use, or to choose not to use, lipid resuscitation therapy (LRT). However, in circumstances where there is serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, LRT is viewed as reasonable consideration for therapy, even if the patient is not in cardiac arrest” [11]. There has been no update issued to this “interim” position statement yet.

Healthcare professionals often consult US Poison Control Centers (PCCs) in the setting of severe overdoses presenting with cardiac arrest or hemodynamic instability. According to the 2011 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS), there were 1,177 deaths attributed to, at least in part, by antipsychotics, cardiovascular drugs, antidepressants, street drugs, and cyclic antidepressants [12]. IFE may play an important role in the treatment of these fatalities. However, it is unclear from the NPDS how often IFE was used in the treatment of patients with moderate-to-severe toxicity or in cases of fatalities.

Our objective was to describe how US PCCs are incorporating IFE as a treatment strategy in the overdose setting. Specifically, we sought to determine PCCs indications for IFE use, recommended dosing, recommended timing, and possible adverse effects according to PCC medical directors.

Materials and Methods

This study received IRB approval. A closed-format multiple-choice survey instrument to evaluate PCC-recommended IFE indications, dosing, and perceived adverse effects was developed by board-certified medical toxicologists, a PCC associate medical director, and PCC staff. Our affiliated PCC medical director was not involved in the design of the instrument as to not influence his potential response to the survey. The survey instrument included general questions about PCC IFE practice patterns, four clinical scenarios to determine PCC recommendations for a 25-year-old male presenting with “cardiac arrest” after an overdose of a single xenobiotic (bupivacaine, verapamil, amitriptyline, or an unknown drug), and four clinical scenarios to determine PCC recommendations for a 25-year-old male presenting with “shock” (blood pressure of 60/30 mmHg with heart rate of 30 bpm) after an overdose of a single xenobiotic (bupivacaine, verapamil, amitriptyline, or an unknown drug). Practice pattern and scenario questions used a four-point response scale from “always,” “often,” “rarely,” and “never.” The instrument was then piloted on the faculty and fellows of a single medical toxicology fellowship and revised. The survey was then sent electronically to every medical director of an accredited US PCC

in March 2011. Addresses were obtained from the American Association of Poison Control Centers listserv. Participation was voluntary and remained anonymous. No compensation was offered for the completion of the survey. Three reminder invitations were sent during the study period. The survey was closed in May 2011. Data were analyzed using descriptive statistics ([Appendix](#)).

Results

Out of 57 PCC medical directors, 45 (79 %) completed the survey. Of the 45 respondents, all felt that IFE therapy played a role in the acute overdose setting. Formal protocols for IFE therapy were used at most (30 out of 45; 67 %) PCCs. The vast majority of PCCs with an IFE protocol (29 out of 30; 97 %) recommended an initial bolus of 1.5 ml/kg of a 20 % lipid emulsion. In addition, 28 out of 30 (93 %) PCCs recommended an infusion of lipids, and 27 out of 28 (96 %) PCCs recommended an initial infusion rate of 0.25 ml/kg/min of a 20 % lipid emulsion.

Most US PCC medical directors (33 out of 45; 73 %) perceived that IFE had no clinically significant side effects at a bolus dose of 1.5 ml/kg (20 % emulsion). The majority of medical directors (44 out of 45; 98 %) felt that the “lipid sink” mechanism contributed to the clinical effects of IFE therapy, but most (26 out of 45; 58 %) felt that there was a yet undiscovered mechanism that likely contributed as well.

In a scenario with “cardiac arrest” due to a single xenobiotic, directors stated that their center would “always” or “often” recommend IFE after overdose of bupivacaine (43 out of 45; 96 %), verapamil (36 out of 45; 80 %), amitriptyline (31 out of 45; 69 %), or an unknown xenobiotic (12 out of 45; 27 %). In a scenario with “shock” (blood pressure of 60/30 mmHg and heart rate of 30 bpm) due to a single xenobiotic, directors stated that their PCC would “always” or “often” recommend IFE after overdose of bupivacaine (40 out of 45; 89 %), verapamil (28 out of 45; 62 %), amitriptyline (25 out of 45; 56 %), or an unknown xenobiotic (8 out of 45; 18 %). Lastly, directors stated that their understanding of IFE was derived mostly from medical conferences (32 out of 45; 71 %) and published human case reports (27 out of 45; 60 %). Published animal studies (22 out of 45; 49 %), online resources (18 out of 45; 40 %), personal experience (14 out of 45; 31), and medical textbooks (2 out of 45; 0.04 %) contributed to their understanding as well ([Fig. 1](#)).

Discussion

Our study confirms that IFE has been incorporated as a treatment strategy by most US PCCs. According to PCC

Fig. 1 Percentage of PCC medical directors who would “always” or “often” recommend IFE

medical directors who participated in our study, practice patterns at most centers are fairly uniform. Currently, the literature supporting the use of IFE in the overdose setting is primarily in the form of animal studies and case reports. While initial data show some clinical benefit, it is unlikely that a robust prospective clinical trial evaluating the efficacy and safety of IFE in the human overdose setting will be completed soon. However, of the 79 % of PCC medical directors who responded, all still felt that IFE played a role in the overdose setting. Interestingly, most PCC medical directors felt that medical conferences and case reports provided the most influence on their understanding of IFE. Until a larger case series or a prospective trial on IFE can be done, it is likely that medical conferences, case reports, and rigorous animal studies will continue to provide valuable insight into the use and mechanisms of IFE.

This study had some limitations. Our response rate was only 79 %. We do not know if the results of this study would have been much different had the remainder of the PCC medical directors responded, but it is important to acknowledge that most of the invited directors participated in this study. In addition, we only surveyed the medical directors of US PCCs. It is impossible to confirm whether poison specialists are conveying recommendations in real time consistent with the recommendations of their own medical directors, so a future study should examine individual specialist recommendations and adherence to their own PCC protocols. Furthermore, there is no way of knowing whether the consulting institutions are following PCC recommendations regarding the use of IFE in the overdose setting and whether the recommendations regarding the use of IFE, or lack thereof, have any clinically impact on patient outcome. One recent study by Darracq et al. demonstrated that consulting institutions used IFE in only 33 % of cases in which it was recommended [13].

It is unknown how many US PCC medical directors are familiar with the ACMT “interim” position statement issued shortly before our study was done or how many of PCC directors are members of ACMT. Interestingly, despite

ACMT’s position that there is “no standard of care” with regard to IFE, most PCC directors in our study feel it plays a role, and dosing recommendations were consistent with ACMT’s recommended dosing guidelines in their “interim” statement. However, no update has been issued to the “interim” statement to date.

There are many other possibilities for future research to clarify the use of IFE in the clinical setting. The ToxIC Consortium is an important collaborative effort that could improve our understanding of IFE benefit and complications [14]. Surveillance of the use of IFE would also be improved if the annual NPDS report included IFE as a treatment modality. It may also be reasonable to present a mock overdose case to a representative sample of specialists in poison information at various PCCs. This may help to further describe whether the IFE protocols are being recommended as intended by the PCC medical directors.

In addition, of the 45 PCC medical directors who felt that IFE played a role in the overdose setting, 15 PCCs did not have “formal protocol.” It would be interesting to know how these programs are advising hospitals to use IFE. Also, since our survey was performed, more data have come out regarding the potential side effects of IFE [15], which may have affected the perception of the safety of IFE by PCC medical directors. There was also discordance in the perception of the medical directors regarding the mechanism of IFE. While the vast majority (44 out of 45; 98 %) believed in the so-called lipid sink mechanism, most (26 out of 45; 58 %) thought that is a “yet undiscovered mechanism” that contributes to the efficacy of IFE. The augmentation of free fatty acid uptake by myocardial cells and the increase of myocardial cell calcium concentration are other proposed mechanisms [10].

In conclusion, IFE therapy is being recommended by US PCCs. Most US PCCs have a protocol for IFE, and the dosing recommendations in these protocols are nearly uniform. Most directors feel that IFE is safe but are more likely to recommend IFE in patients with cardiac arrest than in patients with severe hemodynamic compromise. Medical

conferences and published human case reports currently have the largest influence on directors regarding IFE therapy. Further research and increased surveillance of IFE use in the clinical setting is warranted.

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Conflict of Interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Appendix

Bar graph (Fig. 1) and the survey form.

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