CME Lipid Emulsion for the Treatment of Local Anesthetic Toxicity: Patient Safety Implications

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There is little question that the absolute, scientific "proof" of lipid emulsion's efficacy in reversing local anesthetic-induced cardiac arrest is yet lacking. Such a proof would require prospective, double-blind, placebo-controlled studies in humans, and such studies will thankfully never be performed, for obvious ethical reasons. However, when deciding on the patient safety implications of a novel, potentially life-saving, therapy, one must consider the tenuous and often unknown balance between the purported benefits and potential risks.

BENEFITS

On the one hand, it is obvious from the published case reports (including the three manuscripts in this issue of the journal),[1–3] and the anecdotal "evidence" posted on the web at www.lipidrescue.org, that lipid emulsion (LE) has been used successfully to reverse local anesthetic toxicity. First, it should be noted that it is indeed reversal of "local anesthetic" cardiac toxicity, not just "bupivacaine"-induced cardiac toxicity that responds to LE treatment.[4,5] In fact, there is also published evidence that overdoses with other lipid-soluble drugs (such as bupropion, lamotrigine, verapamil, and clomipramine) may respond equally well to LE therapy.[6–8] Second, recent reports attest to the efficacy of LE therapy in reversing the central nervous system (CNS) toxicity.[3,9] This finding may be equally significant, as the abolition of CNS symptoms may well prevent the progression of CNS toxicity to cardiac toxicity. This has obvious patient safety implications: the CNS toxicity (seizures) can be treated successfully with a number of drugs (benzodiazepines, barbiturates, and isopropylphenol), whereas cardiac toxicity is extremely refractory to most conventional resuscitative techniques and drugs, and previously, institution of cardiopulmonary bypass was the only known treatment. Despite the continued publication of new case reports, however, the ultimate "proof" of efficacy may require many years, if not decades, of LE therapy, given the relatively infrequent incidence of local anesthetic toxicity.

RISKS

On the other hand, the side effects and/or toxicity of LE used as an antidote to local anesthetic-induced toxicity also must be considered. There are no reports suggesting that empiric treatment of local anesthetic toxicity with LE may render the patient less susceptible to advanced cardiac life support rescue. Thus, it may be that even if not directly effective in reversing the local anesthetic toxicity, the empiric use of LE does not appear to pose any acute risks (*primum non nocere*). And although LE is safe and well tolerated in routine clinical practice at doses of 1–2 $g \cdot kg^{-1} \cdot d^{-1}$,[10] administration of LE has been associated with several potential complications: LE infusions modulate cytokine production by mononuclear white cells in response to Candida yeast, suggesting an increased risk of infection[11,12]; LE infusions may produce thrombophlebitis during peripheral IV administration[13]; they may lead to impaired reticuloendothelial

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system function and altered inflammatory responses during long-term therapy[14,15]; they may induce allergic reactions, including anaphylaxis, especially if they contain soy bean oil[16,17]; they may result in pulmonary, splenic, placental, and cerebral fat emboli, especially if the emulsified fat particles are greater than 5 microns in diameter[18,19]; they may cause pulmonary hypertension if administered at rates larger than 100 mg · kg^{-1} · h^{-1} [19]; they may lead to warfarin resistance by facilitating warfarin binding to albumin[20]; they may interfere with extracorporeal membrane oxygenation circuits[21]; they may induce weakness, altered mental status, and seizures in children[22]; and they may induce an increase in the intracranial pressure after a severe traumatic brain injury.[23] Because of the many possible side effects associated with LE administration, the multiple types and combinations of lipid preparations, the various free fatty acid concentrations, and the wide range of lipid globule sizes available, some experts have suggested the adoption of certain pharmaceutical requirements and standards.[24–26] Of all these reported side effects, however, only allergic reactions are likely to arise after acute, short-term administration, such as would occur with administration of LE for rescue from local anesthetic toxicity.

Based on the available evidence, therefore, it would seem imprudent to withhold LE administration in local anesthetic-induced toxicity clinical settings while awaiting scientific proof. This recommendation is not to imply, however, that administration of LE should be the first step in such a clinical setting. Clearly, CNS symptoms such as loss of responsiveness, disorientation, tremors, or seizures must be treated conventionally by ensuring oxygenation and ventilation, securing the airway to protect aspiration of gastric contents in patients at risk, administering anticonvulsants, and instituting advanced cardiac life support protocols in the case of cardiac arrest. Once these conventional treatment modalities have begun, however, immediate IV administration of LE would seem very reasonable and desirable.

Finally, as anesthesiologists, we have always been trained to "prepare for most eventualities" and one of our guiding principles is "vigilance." Based on the available data, it would seem reasonable to have a rescue kit available in any setting in which regional anesthesia is practiced—and in fact, in any location where local anesthetics are administered by any professional, by any route, and in almost any dose. Although cost may be mentioned by some as a consideration when preparing "lipid rescue kits" for all such locations, such concerns must necessarily be secondary to patient safety, and are in fact, trivial: the Intralipid in these kits may be returned to the hospital's central pharmacy to be used for parenteral nutrition before the expiration date, and new Intralipid with a 1-yr shelf life can be restocked in the kit.

These are exciting times, and we may well be witnessing the birth of Panacea.

REFERENCES

1. Warren JA, Thoma RB, Georgescu A, Shah SJ. Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. Anesth Analg 2008;106:1578–80
2. Ludot H, Tharin J-Y, Belooudah M, Mazoit, J-X, Malinovsky J-M. Successful resuscitation after ropivacaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. Anesth Analg 2008;106:1572–4
3. Litz RJ, Roessel T, Heller AR, Stehr SN. Reversal of central nervous system and cardiac toxicity following local anesthetic intoxication by lipid emulsion injection. Anesth Analg 2008;106:1575–7
4. Foxall G, McCahon R, Lamb J, Hardman JG, Bedforth NM. Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. Anaesthesia 2007;62:516–8
5. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia 2006;61:800–1
6. Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, Weinberg GL, Henretig FM. Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. Ann Emerg Med 2007 [Epub ahead of print]
7. Tebbutt S, Harvey M, Nicholson T, Cave G. Intralipid prolongs survival in a rat model of verapamil toxicity. Acad Emerg Med 2006;13:134–9
8. Harvey M, Cave G. Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. Ann Emerg Med 2007;49:178–85
9. Spence AG. Lipid reversal of central nervous system symptoms of bupivacaine toxicity. Anesthesiology 2007;107:516–7
10. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. JPEN J Parenter Enteral Nutr 2006;30:351–67
11. Wanten GJ, Netea MG, Naber TH, Curfs JH, Jacobs LE, Verver-Jansen TJ, Kullberg BJ. Parenteral administration of medium-but not long-chain lipid emulsions may increase the risk of infections by Candida albicans. Infect Immun 2002;70:6471–4
12. Cury-Boaventura MF, Gorjao R, de Lima TM, Piva TM, Peres CM, Soriano FG, Curi R. Toxicity of a soybean oil emulsion on human lymphocytes and neutrophils. JPEN J Parenter Enteral Nutr 2006;30:115–23
13. Smirniotis V, Kotsis TE, Antoniou S, Kostopanagiotou G, Labrou A, Kourias E, Papadimitriou J. Incidence of vein thrombosis in peripheral intravenous nutrition: effect of fat emulsions. Clin Nutr 1999;18:79–81
14. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr 2007;85:1171–84
15. Zoli G, Corazza GR, Wood S, Bartoli R, Gasbarrini G, Farthing MJ. Impaired splenic function and tuftsin deficiency in patients with intestinal failure on long term intravenous nutrition. Gut 1998;43:759–62
16. Andersen HL, Nissen I. Presumed anaphylactic shock after infusion of Lipofundin. Ugeskr Laeger 1993;155:2210–1
17. Weidmann B, Lepique C, Heider A, Schmitz A, Niederle N. Hypersensitivity reactions to parenteral solutions. Support Care Cancer 1997;5:504–5
18. Jasnosz KM, Pickeral JJ, Graner S. Fat deposits in the placenta following maternal total parenteral nutrition with intravenous lipid emulsion. Arch Pathol Lab Med 1995;119:555–7
19. Takifuji K, Tanimura H. Adverse effects of intravenous fat emulsion administration. Nippon Geka Gakkai Zasshi 1998;99:171–5
20. MacLaren R, Wachsman BA, Swift DK, Kuhl DA. Warfarin resistance associated with intravenous lipid administration: discussion of propofol and review of the literature. Pharmacotherapy 1997;17:1331–7
21. Buck ML, Ksenich RA, Wooldridge P. Effect of infusing fat emulsion into extracorporeal membrane oxygenation circuits. Pharmacotherapy 1997;17:1292–5

22. Schulz PE, Weiner SP, Haber LM, Armstrong DD, Fishman MA. Neurological complications from fat emulsion therapy. Ann Neurol 1994;35:628–30
23. Wolf S, Krammer M, Trost HA, Lumenta CB. Lipofundin-induced intracranial pressure rise after severe traumatic brain injury—-a case report. Zentralbl Neurochir 2004;65:81–3
24. Driscoll DF. Lipid injectable emulsions: 2006. Nutr Clin Pract 2006;21:381–6
25. Driscoll DF. Lipid injectable emulsions: pharmacopeial and safety issues. Pharm Res 2006;23:1959–69
26. Driscoll DF. Globule-size distribution in injectable 20% lipid emulsions: compliance with USP requirements. Am J Health Syst Pharm 2007;64:2032–6

