CME Lipid Rescue: A Step Forward in Patient Safety? Likely So!

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In this issue of *Anesthesia & Analgesia* appear three case reports that add to an emerging literature documenting the resuscitation of patients from local anesthetic toxicity by the administration of lipid emulsion.[1–3] These case reports follow the sentinel *clinical* report of Rosenblatt et al.[4] and a subsequent report of ropivacaine toxicity reversal by Litz et al.,[5] that are the culmination of basic science investigation over the past 10 yr. The scholarly underpinning of this therapy has truly been evolving, and because we as doctors are also of the scientific mindset, we should respect and be inspired by the logical maturation of lipid emulsion therapy to the point of its application in the management of local anesthetic toxicity in humans. These case reports are particularly important now, given the prevalence of regional anesthesia and analgesia techniques in contemporary practice, and the fact that they sustain the creative use of a therapy that upholds the clearly established, commanding role that anesthesiology has taken in matters of patient safety. We must all take note of this significant advance in patient care. But first, a bit of the history that puts lipid emulsion therapy into perspective.

Weinberg et al.[6] investigated the possible metabolic connection of toxicity from only 22 mg of bupivacaine in a patient who was subsequently found to have carnitine deficiency. In their experimental model, it was demonstrated that inducing cardiotoxicity was profoundly more difficult in rats that had been pretreated with lipid.[7] This led to intentional studies in rats, and then dogs, which established that animals given pre- or follow-up treatment with lipids for bupivacaine overdose recovered remarkably well.[7,8] These data, originally from 1998,[7] which suggested that lipid infusion had the potential to be a ". . . novel treatment of bupivacaine-induced cardiotoxicity," set the scene for a trial of such therapy in actual patient management (which came 8 yr later!). Rosenblatt et al.[4] reported the first clinical application of such therapy in 2006, and Litz et al.'s[5] report soon followed. Rosenblatt et al. reached the point of preparing to initiate cardiopulmonary bypass in the management of a 58-yr-old man who developed local anesthetic toxicity after an interscalene block with 20 mL 0.5% bupivacaine and 20 mL 1.5% mepivacaine, and who was failing to respond to routine cardiopulmonary resuscitation (CPR) measures. The administration of lipid emulsion was suggested. The classic medications used in resuscitation worked far better after a bolus of 100 mL of 20% Intralipid® followed by an infusion of 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$. Their patient recovered completely, in spite of an impressive history of coronary artery disease (CAD), as did Litz et al.'s (after 40 mL 1% ropivacaine was used in an axillary block in an 84-yr-old woman).

The case reports in this issue not only manifest similar clinical success but also broaden our appreciation for the potential benefits from the application of lipid emulsion therapy beyond that described previously. Litz et al.[1] used 30 mL 1% mepivacaine in a 91-yr-old man with chronic obstructive pulmonary disease, hypertension, CAD, and reflux esophagitis

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in an infraclavicular brachial plexus block before olecranon bursa excision. Neurostimulation was used for nerve localization. Blood return was noted with the first pass of the needle. The primary block was supplemented with 10 mL 1% prilocaine, 5 min after which (and 20 min after the mepivacaine) the patient developed "dizziness, nausea, and agitation." He subsequently lost consciousness and supraventricular extrasystoles and bigeminy were noted. The presumptive diagnosis of local anesthetic toxicity was made and a 1 mL/kg bolus of 20% Intralipid was given, followed by an infusion secondary to persistent extrasystoles. The patient recovered within minutes and the surgery proceeded as the patient had a surgical block. Warren et al.[2] reported a 60-yr-old man with CAD, diabetes, and end-stage renal disease severe enough to mandate dialysis. He developed local anesthetic toxicity after 30 mL 1.5% mepivacaine (with bicarbonate and epinephrine) and 10 mL 0.5% bupivacaine via a neurostimulation and supraclavicular brachial plexus block technique for upper extremity basilic vein fistula revision. This patient developed "labored respiration followed by obtundation" 5 min after the conclusion of the injection. CPR was instituted but the process did not re-establish an effective cardiac rhythm. Ten minutes after the initiation of CPR, an infusion of 20% lipid (250 mL over 30 min) was started, resulting in increasing intervals of a perfusing heart rhythm and, ultimately, the patient's complete recovery. Ludot et al.[3] gave 10 mL 1% lidocaine with epinephrine and 10 mL 0.75% ropivacaine in an anesthetized, 55 kg, 13-yr-old girl in a lumbar plexus block, assisted by neurostimulation. Their patient developed ventricular tachycardia with widened QRS complexes 15 min after the injection. The only treatment provided was 20% lipid emulsion administered as a 3 mL/kg bolus (without a subsequent infusion).[3]

The first two of these new case reports share with those previously published the common feature that the patients had CAD, so it is not surprising that they were considered for regional anesthesia techniques, because many patients with significant comorbidities are so selected (and one wonders whether CAD predisposes patients to local anesthetic toxicity!). With that noted, the patients reported most recently by Litz et al., Warren et al., and Ludot et al. highlight pertinent differences from the previous cases, in that their patients developed local anesthetic toxicity with different regional techniques and drugs.[1–3] Routine procedures for placing the blocks and administering the drugs (frequent aspiration, incremental dosing) were apparently followed, and the doses of local anesthetics used were within guideline values.[9] Furthermore, the clinical presentation of the toxic reactions and the timing of their onset varied, thus emphasizing the diversity of the clinical circumstances in which local anesthetic toxicity may occur and in which lipid emulsion therapy may show its benefit.

Indeed, another interesting observation culled from this short list of case reports is that the time to lipid emulsion administration is getting shorter.[1–5] Rosenblatt et al.'s[4] patient had been in resuscitation approximately 30 min before Intralipid was administered. Warren et al.[2] and Litz et al.[5] started treatment within 10 min of CPR initiation, whereas Litz et al.[1] started lipid therapy within minutes of making the diagnosis of local anesthetic toxicity, as did Ludot et al.[3] This trend is a marked redirection of the initial recommendations made in learned commentaries by Groban, Butterworth and Weinberg (and before any human application), which advocated routine CPR measures and then a trial of lipid emulsion before giving up the resuscitative effort.[10,11] Is this apparently growing impatience based upon the animal data or the evident, rapid recovery of stable cardiac rhythm and/or consciousness seen in these first case descriptions? Is a "why wait" attitude warranted?[10] We gain a modicum of insight in that Litz et al. noted that their previous successful experience with lipid therapy in the rescue of the patient from ropivacaine overdose[5] resulted in their placing Intralipid at sites around their hospital where local anesthetics were frequently used; thus, their emergent use of this therapy in the case report in this issue.[1] Ludot et al.[3] reiterated this theme in stating that the published case reports from 2006 convinced them to place lipid emulsion at clinical sites relevant to their use of local anesthetics. Thus, the treatment was readily available for the immediate management of their pediatric patient.

Perhaps, we will be encouraged to use this seemingly new treatment once we understand the mechanisms that explain the patient's rapid recovery. The predominant view is that the exogenous lipid provides an alternate source for binding of lipid soluble local anesthetics (thus, this is more relevant to bupivacaine, levobupivacaine, and ropivacaine than to mepivacaine and prilocaine).[1,3,4,7,8,10–13] That the lipid may affect the heart in a metabolically advantageous way has also been proposed as a contributory factor.[6–8,10–13]

Even without knowing exactly how the lipid infusion works, the implications for this new management tool are too heartening to ignore. Weinberg et al. make the point that the symptoms of cardiovascular and central nervous system toxicity recur in patients with bupivacaine toxicity, even with conventional treatment, and that after a likely period of central nervous system excitation with or without seizures, the final common pathway of hypotension, bradycardia, and arrhythmias, leading to asystole, ensues.[8,14] Lipid rescue via a bolus and an infusion would seem to mitigate the recurrence of toxic symptoms, and thus aid the resuscitation effort. We must also heed the erudite voice of caution, per Weinberg, that our readily available propofol is not a suitable lipid source for this purpose (let alone the fact that the administration of this cardiac-depressant drug in the face of

cardiovascular collapse is not tenable).[11,14] Admittedly, the most propitious timing for the initiation of lipid therapy, as well as the optimal and maximal doses to be given, the appropriate rate of administration, and the duration of therapy, cannot be established by these case reports, but the trend of using lipid emulsion therapy "early" in resuscitation (and in the patients of Litz et al.[1] and Ludot et al.[3] even before the cardiovascular depression phase of toxicity was manifested), is evident from these reports. That these case reports have blood level data from the events is at first encouraging, but in actuality they are poorly correlated with the clinical findings, suggesting that other factors interact with the onset and presentation of toxicity.[9] Whether the top-up doses used were significant in the generation of toxicity remains a matter of speculation.

We should not be offended by the serendipity of the initial discovery that lipid emulsion "works" in the setting of local anesthetic toxicity. The clinical potential that lipid emulsion therapy has for our patients is being fulfilled, and we can rest assured that the therapy has come from scientific roots. Based upon these realities, will our specialty once again account for an advance that maximizes patient safety? Corcoran et al.[15] showed that academic anesthesiology departments have a "wide variability in preparedness for local anesthetic toxicity and lack of consensus for treatment." They recommended that reasonable solutions to this woeful state of affairs would be to establish protocols for setting-up our work stations and patient monitoring [as Moore advocated years ago[16]], consider carefully the necessary doses and specific local anesthetic drugs to accomplish the clinical task,[9] and create an institutional contact system to make cardiopulmonary bypass readily available in a time-relevant manner. Only a few programs reported that they would consider the use of lipid therapy, which may be more a reflection of the subtlety with which lipid therapy was emerging into a bona fide treatment modality than an active negative choice. The increasing parade of cases in which local anesthetic toxicity has been successfully treated with lipid emulsion urges us to jump on the bandwagon.

The question remains, then, what will now be your response when a patient shows signs and symptoms of local anesthetic toxicity with, or even before, failing CPR? Does the growing number of case reports documenting successful resuscitation via the use of lipid emulsion therapy intrigue you enough to have the drug readily available where blocks are performed in your practice? Will you abide the wise counsel from de Jong that lipid therapy is not a panacea for all forms of toxicity?[17] Will you proceed with the surgical case after your patient has recovered from a local anesthetic overdose by treatment with lipid emulsion? The weight of the evidence, based upon case report quality data, is not overwhelming, but must we wait for more detailed research to specify all of the clinical innuendos for using this treatment?[14] Although the hazards of the doses of lipid given in this therapy are not known, for a patient in the desperate circumstance of local anesthetic toxicity and failing or failed resuscitation, lipid emulsion therapy seems to be a worthy and effective consideration. It would be naive to substitute this treatment for standard CPR, but it is not premature to apply it once it is clear that the likely explanation for a patient's cardiovascular collapse is local anesthetic toxicity and when conventional resuscitation efforts are not generating success. This conclusion is not based on a flash-in-a-pan experiment but rather, on a methodical, scientific evolution of a concept tested in more than one animal model, and now showing dramatic results in a few humans.

We expand our clinical vision by the judicious application of research results. We must stand ready with the most contemporary patient management strategies, since even with prudent technique, including the now prevalent ultrasound guidance, the unexpected may be encountered. The number of instances in which lipid therapy has been used is growing, as tabulated at the registry www.lipidrescue.org© (Copyright, 2007, Guy Weinberg, MD). These clinical scenarios must be reviewed with a very critical eye and yet also gleaned for clinically relevant conclusions that may resolve some of the remaining issues surrounding lipid emulsion therapy. Scientific endeavor will clarify the mechanisms of benefit and the issues of timing, dosing, and the metabolic consequences of lipid therapy. It seems an inescapable conclusion that lipid emulsion therapy works and represents a significant advance in patient safety. We are indeed closer to realizing Weinberg's prediction from 1998 that lipid emulsion could be an effective treatment for bupivacaine overdose and his belief that, "a once feared complication of regional anesthesia may have just become slightly less fearsome".[14]

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