CME Lipid Infusion Therapy: Translation to Clinical Practice

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These are heady days for the regional anesthesia community. Ultrasound technology and continuous-infusion catheters hold the promise for increasing the popularity and utility of perioperative regional anesthesia. This issue of *Anesthesia & Analgesia* includes a series of articles on an apparently effective treatment for the most devastating complication of regional anesthesia: cardiovascular collapse from local anesthetic overdose.[1–4]

The systemic toxicity from local anesthetic overdose was first described by Mayer in a 1928 report of 40 fatalities related to local anesthesia.[5] The risk from modern lipophilic local anesthetics was highlighted by George Albright in a seminal editorial in 1979.[6] Since then, the molecular mechanisms, clinical spectrum, and treatment of local anesthetic cardiac toxicity have been carefully described. Until recently, cardiopulmonary bypass was the only method shown effective in treating refractory cardiac arrest from local anesthetic overdose.[7]

Three laboratory reports over the past decade have shown that infusion of lipid emulsion mitigates otherwise overwhelming bupivacaine toxicity in animals[8,9] and in an isolated rat heart.[10] Rosenblatt et al. subsequently reported rapid resuscitation after lipid infusion in a patient who failed standard advanced cardiac life support measures for cardiac arrest after brachial plexus anesthesia.[11] Similar reports by Litz et al.,[12] Foxall et al.,[13] and Zimmer et al.[14] give added support to the use of lipid emulsion for resuscitation of local anesthetic-induced cardiovascular collapse.

Three cases in this issue of *Anesthesia & Analgesia* further inform our use of lipid infusion and provide novel insights into its mechanism of action, spectrum of clinical use, and evidence of its efficacy in treating local anesthetic toxicity. Warren et al.[4] and Ludot et al.[2] report successful lipid resuscitation using preparations other than Intralipid (Liposyn III 20%, Hospira Inc., Lake Forest, IL, and Medialipid 20% Braun, Germany, respectively). This suggests the salutary effect is indifferent to the brand of lipid emulsion. Ludot et al. report the first use of lipid emulsion therapy in a child. They used a larger bolus dose than previously reported (3 mL/kg) in this 13-year-old patient who quickly recovered from a wide complex ventricular tachycardia. By contrast, the case of Warren et al. showed similarly impressive, but more gradual reversal of electrocardiogram abnormalities, possibly the result of administering lipid only by continuous infusion without the benefit of a lipid bolus. The case of Litz et al. is the first case report describing rapid arousal in a previously unconscious patient and reversal of cardiac arrhythmias with a lipid emulsion. Two of these cases further reinforce the observation from previous case reports that ischemic heart disease and conduction defects predispose to local anesthetic cardiac toxicity.[1,4]

Litz et al.[1] report pharmacokinetic data with a mechanistic interpretation. I congratulate them for having sufficient presence of mind in a crisis to collect serum specimens before and after lipid infusion. They show that serum levels of mepivacaine decreased more rapidly after lipid infusion than predicted by the published half-life and argue this observation favors the "lipid sink" hypothesis of lipid rescue.[9] The lipid sink theory holds that lipophilic local anesthetic molecules partition into a lipemic plasma compartment making them unavailable to the tissue. This is an attractive

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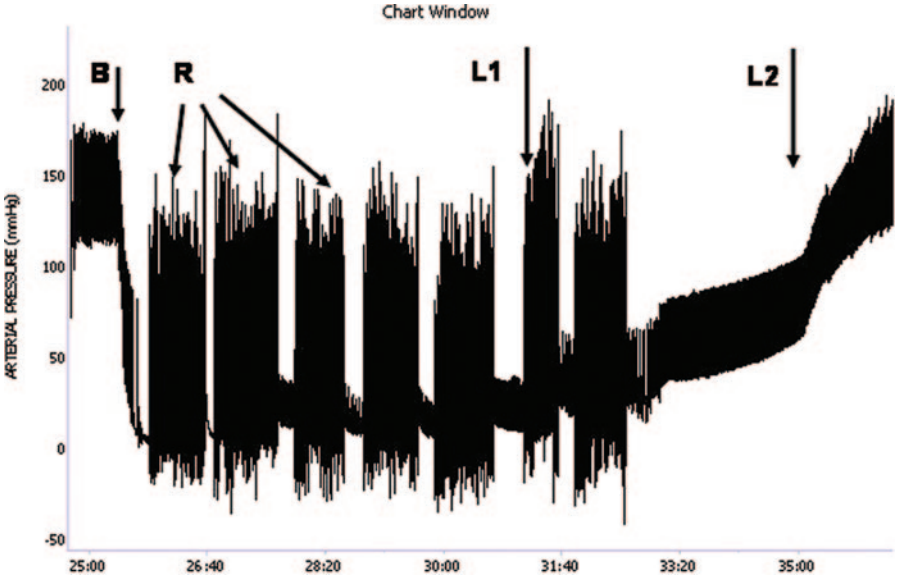

Figure 1. Hemodynamic response to lipid infusion. The arterial pressure trace of a rat is shown over approximately 12 min. B, IV injection of 20 mg/kg bupivacaine over 20 s. R, resuscitation by closed chest compression. L, infusion of 30% soybean oil emulsion, 5 mL/kg, over 10 s. Recovery of hemodynamic profile occurs after second lipid bolus, L2.

hypothesis by virtue of its conceptual simplicity. However, it predicts that total plasma concentrations of local anesthetic should increase after lipid infusion, as the local anesthetic becomes bound into plasma lipids. If, as observed in the case reported by Litz et al., lipid rapidly reduces serum anesthetic levels, then the mechanism is one of increasing metabolism, distribution, or perhaps partitioning of local anesthetic away from receptors into lipid within tissues, not merely shifting equilibrium away from the end-organ to the plasma.

It is difficult to envision how a few tablespoons of IV lipid emulsion could alter equilibration across the many intervening tissue diffusion barriers rapidly enough to account for prompt reversal of bupivacaine toxicity. A salutary effect on oxidative metabolism might explain the swift, cardiotonic effect of lipid infusion seen clinically and in the laboratory. Bupivacaine potently inhibits fatty acid transport at the inner mitochondrial membrane. It has been proposed that lipid could act by countering this brake on the oxidation of the heart's preferred fuel.[15] The salutary effect of insulin-glucose therapy on bupivacaine cardiac toxicity[16] suggests metabolic inhibition may be a critical component of bupivacaine-induced cardiac depression.[17] Consistent with the metabolic hypothesis, Stehr et al.[18] have shown that lipid infusion is a positive inotrope in isolated heart and reverses bupivacaine-induced cardiac depression at lipid levels less than those needed to reduce aqueous bupivacaine concentration. Hence, metabolic, direct inotropic, or other physiological effects may contribute to lipid-mediated resuscitation.

Optimizing the treatment of local anesthetic toxicity requires comparing various modes of therapy. A trial by Mayr et al.[3] in this issue of *Anesthesia & Analgesia* compares lipid infusion to vasopressors in a porcine model of bupivacaine overdose with hypoxic cardiac arrest. They found that all pigs in the group treated with epinephrine plus vasopressin showed return of spontaneous circulation, whereas none survived after a single bolus of lipid plus a continuous infusion. These results are inconsistent with the results of rat and dog studies of lipid emulsion infusion[8,9] and contradict recent findings from our laboratory.[19] The lack of efficacy for the lipid may reflect differences in the experimental design among the studies. The Mayr et al. study achieved cardiac standstill by prolonged asphyxia, a condition for which use of lipid was never recommended. A larger lipid dose (in mL/kg) than used by Mayr et al. has been shown to be effective rescuing rats that received closed chest compressions after massive bupivacaine overdose.[9] Perhaps, additional lipid boluses (e.g., Fig. 1) might have yielded a successful recovery in their study. Given the many clinical reports of successful lipid rescue after failed resuscitation with epinephrine, the findings of Mayr et al. should not discourage the use of lipid, but indicate that lipid therapy should supplement conventional cardiovascular support.

How early in the clinical progression of local anesthetic toxicity should we use lipid? A lack of outcome data provided the rationale for my earlier recommendation that lipid infusion be delayed until standard resuscitative measures failed.[20] This seemed reasonable a year ago with only one case report of successful lipid rescue resuscitation and no safety studies of rapid lipid infusion. As additional data have become available, it appears irrational to wait until asystole before administering a lipid bolus. Once signs of local anesthetic toxicity are manifest, the accumulating evidence supports early use of lipid infusion to attenuate progression of the local anesthetic toxic syndrome.

The clinical community is responding to the increased data supporting lipid therapy. In the survey published by Corcoran et al. in 2006, 74% of responding American academic anesthesia departments indicated they would not use lipid to treat bupivacaine toxicity.[21] By contrast, this year, the Association of

Anaesthetists of Great Britain and Ireland has sent its members recommendations for treating local anesthetic toxicity that prominently feature lipid emulsion infusion. More information about implementing lipid therapy can be found at the educational website: www.lipidrescue.org.

Although cardiovascular compromise during regional anesthesia is rare,[22] the rhythms shown at 8, 9, and 13 min in Warren et al., or panel A of Ludot et al.'s Figure 1 should make any clinician glad there is a potential antidote. The recent report of successful lipid resuscitation with full neurological recovery after 70 min of bupropion-induced pulseless electrical activity suggests that this therapy may be useful to treat overdoses of drugs other than local anesthetics.[23] However, the anesthesiologist who first considered using lipid in that case had to fetch it himself from the pharmacy (personal communication, Dr. Archie Sirianni, Philadelphia, PA). Given the evidence of benefit, and the lack of apparent risk, it seems prudent to stock lipid emulsions in settings where overdoses are treated (operating room, postanesthesia care unit, emergency room) to avoid wasting precious time at a critical moment in patient care. Future case reports and animal studies will help to evaluate the timing, dose, and clinical utility of lipid resuscitation.

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