Lipid Emulsion in Local Anesthetic Toxicity

Long-winded, Rude, and Right

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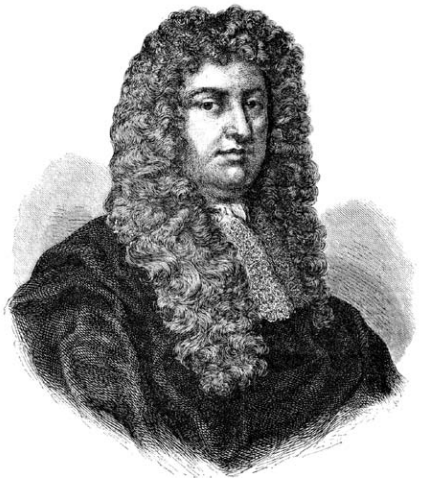
LORD Cyril Asquith, son of a British Prime Minister, and himself an English Law Lord, once remarked "A Judge of the first instance should be brief, courteous, and wrong. This is not to imply that the Judge of Appeal should be long-winded, rude and right, for this is a privilege confined to the House of Lords." Such sentiment appears apt when weighing our evolving understanding of the antidotal mechanism of lipid emulsions. Initial thinking attributed recovery from cardiotoxicity to sequestration of lipophilic local anesthetics into a newly created intravascular lipid phase—arise the "lipid sink." This theory was altogether brief, courteous in its inherent simplicity, and if not entirely wrong, then at very least only a partial truth. No "truth" can ever be thought robust until the passage of time has presented new data that it must attempt to explain. And with the passing of time, and the diligent work of a number of investigative groups, our comprehension of the pharmacokinetic and pharmacodynamic sequelae of infusing a concentrated triglyceride microemulsion in local anesthetic systemic toxicity (LAST) has become clearer. The underlying mechanism(s) of lipid emulsions have been demonstrated as "long-winded," in that they are multiple and multimodal. Rude, for their inherent complexity has required complicated modeling techniques to decipher. Ultimately, however, they are far more right than our original musings.



"No 'truth' can ever be thought robust until the passage of time has presented new data that it must attempt to explain."

It has been nearly two decades since Weinberg *et al.*[1] published his original findings showing a rightward shift in survival curves for bupivacaine-intoxicated rats treated with a lipid emulsion. The intervening period has seen investigative efforts focus on the underlying mechanistic actions of lipid with simple hemodilution, direct cardiotonic effects, and partitioning/augmented redistribution, all being proposed as potential therapeutic actions. Perhaps due to the inherent simplicity of understanding, and comparative ease of investigation, the sink theory garnered the most initial attention. Not surprisingly, the seemingly generic purported benefits of lipid sequestration were also embraced by clinicians treating overdoses of alternative lipophilic cardiotoxins, with efficacy reported in animal models and human cases.[2] Misgivings as to the adequacy of the sink theory, nevertheless, have abounded since the origins of the hypothesis. Total myocardial bupivacaine content decreased by only (an albeit significant) 20% more than controls in isolated rat hearts perfused with lipid in the seminal work of Weinberg *et al.*,[1] raising questions even then of additional synergistic mechanisms. Similarly, in models of tricyclic antidepressant cardiotoxicity, engineered liposomal formulations (demonstrated as superior detoxification vehicles *in vitro*) perform less well than 20% lipid emulsion in effecting cardiovascular recovery in whole animals.[3] In the current issue of the journal, Dureau *et al.*[4] further explore potential mechanistic contributions of administered lipid emulsion in healthy volunteers undergoing infusions of ropivacaine and levobupivacaine. They are to be applauded for conducting a volunteer study to a clinically defined endpoint in a field wherein prospective human trials are, for obvious reasons, problematic. Their results are informative.

In a randomized crossover design, these authors investigate the effect of early administration of intravenous lipid emulsion on time to first-onset neurotoxicity with concurrent infusion of ropivacaine or levobupivacaine. The study proves negative for the primary outcome—no

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difference in tolerated dose of either local anesthetic was reported. A lesser reported C_{max}, and increased central volume of distribution, does however support modest favorable alterations in pharmacokinetic parameters after lipid infusion. While seemingly at odds, the tension between the primarily powered symptomatic endpoint and the pharmacokinetic data may not be as complex as it seems at first glance. Lipid emulsions are elegantly described by Mazoit *et al.*[5] as entropic binders—no energy is expended associating with the lipophilic molecules they entrap. Absence of any energetic commitment makes lipid emulsions free in their association and dissociation with these compounds—when a depot of equal affinity arises, lipid emulsion puts no energy into the fight for its lipophilic partner. The sum of the pharmacokinetic effects of lipid emulsion on the time to developed neurotoxicity during local anesthetic infusion must involve a balance between potentially retarding initial distribution to highly perfused tissues, perhaps no great "entrapment" on circulation through well-perfused lipophilic brain tissue, and increased delivery to lesser perfused adipose depots. It is perhaps not surprising that the sum of these effects on time to onset of neurologic symptoms led to a result favoring the null.

The most significant clinical complication of local anesthetic toxicity is cardiovascular collapse, a circumstance relatively impenetrable to structured human study. It also represents a distinct pharmacokinetic situation when considering infusion of lipid emulsion; local anesthetic has already intoxicated the heart in LAST, and the pharmacokinetic benefit of introduced lipid would be local anesthetic removal rather than to retard further deposition. The authors appropriately go on to model the effect of bolus lipid administration after extravascular administration of ropivacaine and levobupivacaine using parameters returned from their data set. These simulations again suggest significant, yet modest, benefits of lipid emulsion. Extrapolated maximal local anesthetic concentrations at cardiotoxic dosing appear lesser for levobupivacaine than for ropivacaine, with maximal benefit expected at high and rapidly rising concentrations—exactly the situation seen in LAST.

Utilization of powerful modeling techniques has greatly advanced our understanding of the effects of lipid microemulsions in local anesthetic toxicity. Such models enable integration of previously compartmentalized concepts and postulated mechanisms into a coherent whole. Using a physiologically based pharmacokinetic–pharmacodynamic model, Fettiplace *et al.*[6] demonstrated the rapid recovery of hemodynamic stability after bupivacaine overdose in rats to be dependent on a direct cardiotonic action, coupled with both volume and sink effects acting in concert. The same investigative group subsequently provided the most comprehensive explanation for the effect of triglyceride microemulsion in bupivacaine pharmacotoxicity by combining physiologic parameters with pharmacokinetic data obtained from bupivacaine-intoxicated rats in an *in silico* computational model.[7] This elegant work demonstrated a rapid detoxifying effect of lipid emulsion, acting primarily on key end organs including the heart and the brain—dependent on the partitioning effect of introduced lipid. Then once cardiac drug concentration fell below a threshold (consistent with channel dissociation thresholds), the emulsion produced a cardiotonic effect through the combined actions of volume expansion and direct inotropy. Subsequently, increased blood carriage combined with improved cardiac output was demonstrated to enhance redistribution of drug to nonessential depot organs and sites of metabolism. Without the assistance of complex modeling technologies, such explanations would be near impossible to elucidate in detail. The work of Dureau *et al.*[4] lends support to this assembled whole hypothesis of lipids' detoxifying activity, their human data demonstrating a small, yet significant sink effect of lipid.

Perhaps the next step in our understanding of the action of triglyceride emulsions is to more fully elucidate the inotropic mechanism induced following injection. Direct utilization as energy substrate, augmented mitochondrial processing, and effects on nitric oxide modulation have all been proposed. What is not known, however, is the exact nature of cardiac toxicity amenable to lipid-mediated inotropy. Greater understanding here would allow for more informed recommendation around wider application of lipid emulsions beyond the field of anesthesia—what toxic drugs recreate the same cardiac milieu wherein a lipid emulsion may augment cardiac function and which might better respond to a pure targeted detoxification vehicle (*e.g.*, pH-gradient liposomes).

For now, it seems that our initial thoughts regarding the partitioning effects of lipid emulsion may not have been completely wrong. Perhaps just that in its brevity and courtesy, a sole "sink" mechanism required added judgments, gained from work such as that of Dureau *et al.*, to become complete.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From Chloroform to Clio and Calliope, Liebig's Muses of History and Epic Poetry

On this Italian card advertising a company named after chloroform pioneer Justus von Liebig (1803 to 1873), a seated Muse Clio (*right*) records history upon a writing tablet with her stylus. As the Muse of History, Clio governs historical collections, such as the Wood Library-Museum of Anesthesiology. However, in ancient Greece, long chronicles of names and events were frequently mastered in the semimusical oral tradition of ancient Greek verse. Homer's *Iliad* and *Odyssey* invoked a goddess, perhaps the Muse of Epic Poetry, Calliope ("beautiful voiced"). She is frequently depicted as a belaureled standing figure (*left*) clutching her iconic scroll. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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