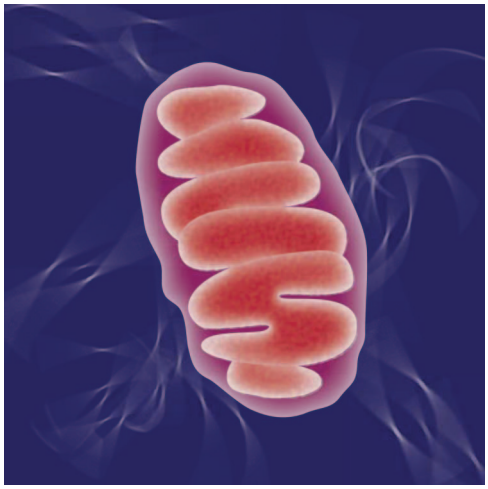
From Bedside to Bench and Back

Perfecting Lipid Emulsion Therapy for Local Anesthetic Toxicity

THE first clinical use of intralipid as a rescue treatment for refractory cardiotoxicity associated with local anesthetic occurred in 2006.[1] Until then, the only management options for this notoriously difficult-to-treat complication were purely supportive: either cardiopulmonary resuscitation or institution of cardiopulmonary bypass.[2] Numerous case reports followed that first use, and treatment with lipid emulsion therapy has been incorporated into current guidelines for the management of local anesthetic systemic toxicity.[3] The development of lipid emulsion therapy is a fascinating story and highlights how an unexpected clinical observation can spawn important basic research that ultimately leads to a new, more effective therapy. This "bedside-to-bench-and-back" approach is essential when working with rare but severe problems because sufficient clinical data often are unavailable. The article by Li *et al.*[4] continues this work by investigating the mechanism by which lipid emulsion therapy reverses bupivacaine's cardiotoxic effects. They report on the impact of adding medium-chain triglycerides (MCT), which have a theoretically more favorable profile for supporting myocardial metabolism, to standard therapy with long-chain triglycerides (LCT) on the success of both the initial resuscitation and recurrence of asystole in rats with bupivacaine-induced cardiotoxicity.



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Although adverse cardiac effects associated with etidocaine and bupivacaine had been reported shortly after their clinical adoption in the 1960s, the effects initially were attributed to either inadvertent subarachnoid injection or expected physiologic effects.[5] It was not until a 1979 case report of a healthy young man who abruptly experienced seizure and ventricular fibrillation resistant to standard therapy after caudal injection of 25 ml etidocaine (1%) that the potential for prolonged myocardial toxicity was acknowledged.[6] An editorial published later that year reported five additional cases.[7] Although the editorial was widely criticized,[5] the experimental studies that followed confirmed several molecular mechanisms that underlie the toxicity of these agents.[8] Resuscitation after these events generally was prolonged and resistant to conventional treatment, but patients often made a full recovery, presumably after plasma concentrations of the offending agent dropped below a critical threshold.

The development of lipid emulsion therapy had its beginnings in 1997, when Weinberg *et al.*[9] reported unexpected bupivacaine-associated cardiotoxicity in a patient with a metabolic disorder. Questions from this case led to a series of experiments using lipid infusions in animal models, which were expected to reduce the threshold for toxicity. However, instead of increasing sensitivity to bupivacaine, as had been anticipated, lipids were found to have a protective effect.[10] With this observation in mind, the researchers hypothesized that the creation of an intravascular lipid compartment separate from the plasma phase sequestered bupivacaine and allowed the effective plasma concentration to decrease. This "lipid sink" theory has an appealing simplicity and is well supported by experimental data.

However, bupivacaine has been shown to have toxic effects at multiple sites within cardiac myocytes.[8] In addition to its well-described effects on ion channels, the inhibition of fatty acid transport into mitochondria is particularly relevant. In a series of subsequent experiments, Weinberg *et al.*[11] demonstrated that bupivacaine toxicity inhibited carnitine-acylcarnitine translocase, one of the enzymes necessary for the transport of fatty acids into mitochondria. Based on this observation, they proposed an additional mechanism by which lipid therapy could reverse bupivacaine toxicity. According to this "lipid flux"

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theory, the large increase in lipid concentration overwhelms inhibition of carnitine-acylcarnitine translocase and provides better substrates for metabolism within the cardiac myocyte. This effect is also consistent with more general models of myocardial ischemia or reperfusion injury, where lipid therapy has shown benefit through modulation of specific enzyme-salvage pathways and mitochondrial permeability.[12]

The work by Li *et al.* attempts to isolate effects of the "lipid flux" hypothesis from those of the "lipid sink" hypothesis. By using MCT, which are not dependent on carnitine-acylcarnitine translocase for transport into the mitochondria, the researchers evaluate the impact of increasing the fatty acid supply to the mitochondria by a mechanism that is independent of bupivacaine-induced toxicity. The study also evaluates a potential refinement to the current treatment recommendations that clearly have efficacy but are otherwise difficult to study under clinical conditions. MCT have been used successfully during resuscitation,[13] which raises an important question: which lipid is best? Because there is a theoretical advantage to mitochondrial metabolism with MCT, should we change the current recommendations? If these events occurred more frequently or at least were more predictable, a randomized controlled trial might be warranted, but such study seems impractical in this case. The answer likely will need to come from research at the bench.

The results of Li *et al.* show no significant difference in initial resuscitation when using a combination of MCT and LCT *versus* LCT alone, but they found a significantly higher rate of recurrent asystole associated with the MCT-LCT group. Consistent with this finding, they also noted generally higher concentrations of bupivacaine in the MCT-LCT groups *versus* LCT groups over time, with a remarkable increase in bupivacaine concentration between 30 and 60 min after the start of treatment. This increase in plasma concentration also coincides with the recurrence of asystole in the MCT-LCT group during in the first 45 min of treatment. These results appear to favor lipid sink and discount the lipid flux hypothesis. However, the study has some limitation that make it difficult to completely discount the significance of mitochondrial fatty acid metabolism. MCT have a shorter half-life than do LCT (17 *vs.* 33 min), but the volume of the initial lipid bolus and subsequent infusion rates were the same in each group. In effect, the size of the lipid compartment in the MCT-LCT group decreased in size over time compared with that of the LCT group. Bupivacaine could have been released back into plasma more rapidly as MCT were metabolized, resulting in a higher rate of asystole. Controlling for the effective size of the lipid compartment in each group may lead to a different result.

Based on the main findings of this study, it would appear LCT are superior to MCT-LCT for treating bupivacaine cardiotoxicity. However, there are other subtleties in the data that hint MCT might show some small advantage in a study with greater statistical power. For example, the MCT-LCT group showed a shorter (but not statistically significant) time to first heartbeat and return of spontaneous circulation. There was also a consistent trend (but no statistical significance) toward higher adenosine triphosphate, adenosine diphosphate, and adenosine monophosphate concentrations in the MCT-LCT group. If these observations persisted in an appropriately powered study, it would lend support to a lipid flux mechanism, although it appears to be a small effect compared with the lipid sink.

Thankfully, local anesthetic toxicity is a rare complication, but given the number of patients receiving epidural and regional anesthetics each year, a large population is at risk. With careful clinical observation, diligent bench work, and the willingness of clinicians to try a therapy that has a theoretical benefit, we now have an effective treatment for a potentially devastating complication. However, there is still room to refine and optimize this treatment, a process that undoubtedly will require additional iterations between the bench and bedside.

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