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. Until then, the only management options for this notoriously difficult-to-treat complication were purely supportive: either cardiopulmonary resuscitation or institution of cardiopulmonary bypass. 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. 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 are often unavailable. The article by Li et al. 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.

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. It was not until a 1979 case report of a healthy young man who abruptly experienced seizure and ventricular fibrillation resistant to standard therapy 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. 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. 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. 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. 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” potential for prolonged myocardial toxicity was acknowledged. An editorial published later that year reported five additional cases. Although the editorial was widely criticized, the experimental studies that followed confirmed several molecular mechanisms that underlie the toxicity of these agents. 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.

theory, the large increase in lipid concentration overwhelms in-
hibition of carnitine-acylcarnitine translocase and provides bet-
ter 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 path-
ways 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-acylcarni-
tine translocase for transport into the mitochondria, the re-
searchers 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 poten-
tial 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 recom-
mandations? 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 ver-
sus LCT alone, but they found a significantly higher rate of
recurrent asystole associated with the MCT-LCT group. Con-
sistent with this finding, they also noted generally higher con-
centrations of bupivacaine in the MCT-LCT groups versus
LCT groups over time, with a remarkable increase in bupiva-
caine 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
discern the significance of mitochondrial fatty acid metab-
olism. 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 car-
diotoxicity. However, there are other subtopics 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

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