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Cover story

Triglyceride micro-emulsion for detoxification of acute pharmacotoxicity

It was first observed in 1998 that a triglyceride micro-emulsion could rapidly reverse cardiac arrest associated with local anesthetic overdose [1]. This observation was quickly translated into clinical use because of the availability of triglyceride micro-emulsions, such as Intralipid®, which are approved by the FDA as both parenteral nutrition solutions and liposomal delivery systems. The translation occurred with only a handful of basic research papers without a well-defined mechanism. Without a clear mechanism for its antidotal effects, however, the use and the extensibility of triglyceride micro-emulsions will be limited. Within the field, many mechanisms have been proposed, and the most often cited and studied is the lipophilic buffering theory, commonly referred to as the "lipid sink". The intravascular triglyceride micelles are thought to scavenge the toxin away from the sites of action by providing a lipophilic space for these drugs to partition into. This capture theory is intuitive, since Intralipid® has been employed in the converse setting as a delivery agent for drugs like propofol. However, the lipid sink lacks robust supporting evidence. Importantly, no *in vivo* evidence controls for lipid effects across a range of myocardial drug concentrations. Thus, questions around resuscitation with lipid emulsion have not been resolved.

In the current issue, Dr. Weinberg and his colleagues provide concrete (*in vivo* and computational) evidence for both dynamic scavenging and cardiotonic effects that reconcile the prior conflicting results [2]. They demonstrate that the key to accelerating recovery from acute pharmacotoxicity is facilitated redistribution by collective scavenging and cardiotonic effects. The authors characterized the pharmacokinetics of radiolabeled-bupivacaine, a long-acting, cardio-depressant local-anesthetic, both in the presence and absence of treatment with the triglyceride micro-emulsion. The team further probed various mechanistic possibilities using a computational ("*in silico*") model. They demonstrated that the infused micro-emulsion effectively partitioned bupivacaine out of tissue and into blood. This increased drug concentration in whole blood at analogous organ concentrations when compared with controls. The inverse effect was observed when looking at just plasma or red cells, indicating that lipid infusion shifted the drug out of both tissue and plasma. This scavenging produced discordant effects on pharmacokinetic parameters, i.e., accelerated redistribution out of target organs and the plasma with increased content of the drug in whole (lipid-laden) blood.

The temporal offset of physiologic recovery between the two groups confounded certain comparisons. Michael Fettiplace, a doctoral candidate with the Weinberg team, contributed a solution to this problem by eliminating time as a factor and examining the effect of triglyceride micro-emulsion on hemodynamics across a range of cardiac bupivacaine concentrations. This lead to the key insight that cardiac output did not recover until myocardial bupivacaine concentration fell below ~100 nmol/g which coincides with the thresholds for blocking ionotropic channels (e.g., Ca^{2+} and Na^{+}) in the heart. Below this threshold, the micro-emulsion produced a strong inotropic effect confirming earlier evidence that a cardiotonic effect contributes to the rapid hemodynamic recovery [3]. The threshold-based effect implies that removal of drug is the primary event in recovery, thus indicating the importance of scavenging. Of potential clinical relevance is that the micro-emulsion partitions bupivacaine preferentially at earlier time points when drug concentrations are highest, indicating the dynamic aspect of the scavenging effect and implying a benefit to early treatment.

The work of the Weinberg team provides a clear mechanism to support the clinical effectiveness of this treatment and offers many options for improvement and optimization. Triglyceride micro-emulsions are currently employed for detoxification, because they have a 50-year track record of safety. As both drug-delivery and drug-capture agents, however, triglyceride micro-emulsions are inefficient due to their non-specificity and a short circulating time. Improved scavenging systems could sequester drugs more effectively. For instance, Intralipid® is an emulsion with a particle diameter of ~300 nm and approximately −40 mV zeta potential. Increasing the surface area further with even smaller particles and/or changing the surface charge might improve the scavenging capacity and specificity. The use of drug-loaded scavengers offers the possibility of treatment/scavenging combinations. The elucidation of a mechanism provides an opportunity for the drug delivery community to refine the next generation of bio-detoxification agents [4].

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