Limits to Lipid in the Literature and Lab: What We Know, What We Don't Know

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There is a normal trajectory to the early life of any new therapy: general reluctance to embrace a treatment gives way, over time, to acceptance when there are supporting data or at least good clinical results. The free donuts, coffee, and pens that pharmaceutical company representatives (used to) offer are an attempt to accelerate this process. Then, at some point, glitches begin to appear, the luster might fade and time is needed to assess the treatment's true clinical utility and, ultimately, its longevity.

After a latent period of nearly a decade, lipid emulsion therapy has finally gained acceptance as an effective treatment for local anesthetic-induced toxicity.[1] In this case, laboratory data[2,3] and the outcomes, not donuts, made the difference . . . and there are some very good outcomes indeed. Published reports of dramatic saves,[4,5] including many in this journal,[6–8] provided support for the efficacy of lipid infusion in a setting in which patients' lives and clinicians' equanimity are in extreme jeopardy. However, as expected, the enthusiasm engendered by these reports must inevitably be tempered by observations that the method, not surprisingly, has limitations. A case report of recurrent cardiac compromise 40 min after successful lipid resuscitation and a study showing that lipid does not revive the asphyxiated heart, both in this issue of *Anesthesia & Analgesia*, suggest there are added levels of complexity to the lipid narrative. I expect to read of other instances in the future in which the promise of lipid emulsion as a panacea is not fulfilled. Fortunately, proper interpretation of such findings will lead to a better understanding of the mechanism(s) and role of lipid in resuscitation and thereby contribute to improved patient safety.

Harvey et al.[9] report that lipid emulsion infusion impairs recovery of spontaneous circulation in an ovine model of asphyxial cardiac arrest. This experiment asks the question: "Does lipid work in all resuscitation scenarios? " The possibility that lipid exerts a direct cardiotonic or metabolic advantage to the heart is plausible since lipid-based resuscitation often succeeds after standard resuscitation medications have failed. Given that cardiac arrest is most often the result of an ischemic insult, the easiest, most clinically relevant model to test the hypothesis would involve an ischemic or asphyxial arrest. The study of Harvey et al. clearly indicates that lipid impairs return of cardiac function in the setting of profound hypoxia, as only 1 of 11 lipid-treated subjects versus 7 of 12 control animals met criteria for return of circulation. Although largely unanticipated, this finding is in concert with that of Mayr et al.,[10] who compared lipid versus vasopressors in a porcine model of bupivacaine overdose plus asphyxia. They reported that 0 of 5 lipid-treated animals were revived, whereas five of five of pigs receiving a combination of epinephrine and vasopressin had return of spontaneous circulation. However, before treatment, all animals were rendered severely hypoxic, a confounding variable that precludes the unambiguous assessment of lipid in treating bupivacaine overdose *per se*. Nevertheless, the difference in outcomes suggests that adding lipid in the setting of asphyxia impaired recovery.

The study of Harvey et al. also has an important confounder in that all animals received two boluses of epinephrine as part of the resuscitation.

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Weinberg et al.[11] showed in a rodent model of bupivacaine overdose that similar (per kg) doses of epinephrine impair cardiac function and metabolic indices during resuscitation. Therefore, as the effect of lipid alone was not tested, one cannot exclude the possibility that the combination of epinephrine and lipid given by Harvey et al. was in itself injurious.

The overarching theme of both Mayr et al. and Harvey et al. was the element of asphyxia, and it appears that in this context lipid is potentially injurious to recovery of cardiac function. However, most (four of seven) of the control animals scored by Harvey et al. as having developed return of spontaneous circulation by 14 min were dead by 50 min. Hence, there was no difference between the saline and lipid-treated animals with respect to lasting survival. This late failure is consistent with the results of Weinberg et al. in which epinephrine-treated animals had elevated systolic pressures early in the resuscitation sequence but by 10 min exhibited poor tissue perfusion and cardiac output. It is also consonant with a recent clinical study of out-of-hospital cardiac arrest in which asphyxia presumably approaches 100%. Gueugniaud et al.[12] found that after failing cardioversion, patients receiving epinephrine, with or without vasopressin, had early response rates (27% survival to hospital) that far exceeded later survival (1% survival to hospital discharge), results eerily similar to those of Harvey et al. Thus, the findings of Harvey et al. suggest that lipid's failure to achieve sustained recovery from ischemic arrest is no different from other (laboratory or clinical) scenarios in which asphyxia dominates.

The fascinating case report of Marwick et al.[13] illustrates two more potential limitations of lipid infusion therapy. First, they report that severe bupivacaine toxicity recurred after an initially successful lipid resuscitation, 40 min after stopping the emulsion infusion. This aspect of their report is highly reminiscent of our experience in the laboratory when arterial blood pressure and heart rate often flag a few minutes after an initial return of spontaneous circulation. We were able to prevent this by following the lipid bolus with a continuous infusion, which seemed to support the blood pressure. This was incorporated into subsequent clinical recommendations for lipid administration. However, an adequate explanation is lacking, because a simple partitioning effect (e.g., lipid sink) predicts that a single, adequate dose of lipid should suffice. Nevertheless, in both our rodent and canine models, the immediate postresuscitation blood pressure seems to be directly related to the rate of lipid infusion, an observation more indicative of a direct inotropic or metabolic effect. There are preliminary laboratory data to support the idea.[14]

This case is similar to that reported by Levsky and Miller[15] in that both patients exhibited prolonged, persistent cardiovascular compromise due to bupivacaine toxicity. The patient described by Levsky and Miller received a very low dose of bupivacaine but developed bradycardia and hypotension leading to asystole that was treated with epinephrine (2 mg) without lipid. Hypertension (201/129 mm Hg) was followed by persistent hypotension and pulmonary edema, requiring adrenergic support and mechanical ventilation for 24 h. This clinical arc is reminiscent of the results described by Weinberg et al., in terms of both the late hypotension after epinephrine and the progression to severe pulmonary edema, observed in four of five rats receiving epinephrine. The important point illustrated by both cases is that lipophilic local anesthetic-induced cardiac toxicity can be protracted and, as shown by Marwick et al., this can occur even after lipid infusion. Therefore, it is important to monitor these patients for a considerable period after such an event and to have access to sufficient lipid emulsion for repeated boluses or prolonged continuous infusion, possibly as much as 1 L of 20% lipid for an adult.

Marwick et al. also found that their patient developed elevated serum amylase. Although not previously reported, this is not a surprising occurrence because the severe hyperlipidemia, expected after acute lipid infusion, can obviously provoke acute pancreatitis. Fortunately, the patient exhibited no clinical signs of pancreatitis and the hyperamylasemia did not impact the clinical outcome. However, it points out that 1) we should monitor for signs of pancreatitis after lipid-based resuscitation, and 2) there is very likely a limit to the volume of lipid that can be safely infused acutely. However, the precise limit and the adverse effects of exceeding it are unknown. Therefore, there is an unquestionable need for studies to determine the upper limit for safe, acute lipid emulsion infusion. Safety concerns are an important potential limitation to the use of lipid in resuscitation. This is particularly true in the setting of a prolonged resuscitation in which the patient could receive very large lipid volumes and particularly in the question of early treatment with lipid in which theoretical benefits must be weighed against largely unknown risks.

There is plenty more to learn about the clinical use of lipid emulsion and continued, critical reading of the literature is required. Challenges to improving our use of this method include defining the optimal treatment regimen and emulsion formulation, identifying the best metrics to assess recovery, elucidating the underlying mechanism(s), categorizing potential complications, and predicting which drug overdoses it can (and cannot) treat. These issues must be addressed by rigorous investigation. However, even the literature does not always offer an easy or clear path to understanding. Clinical reports are subject to positive bias but, as lipid-based resuscitation becomes more commonplace, clinicians are less likely to report cases and editors are less likely to publish them, even those with excellent outcomes. On the obverse, as failures are

reported, the actual cause(s) for lack of recovery will rarely be clear cut. It will be easy to invoke a failure of lipid emulsion, but too many other factors contribute to a poor outcome to know which or what combination of system, patient, or clinical elements impeded resuscitation. Even in the controlled laboratory environment, as the studies by Harvey et al. and Mayr et al. indicate, we can have difficulty sorting out the causes of a failed resuscitation.

Dr. Lloyd Smith, my mentor of a few years back, explained that exhilaration is the feeling you get with a great idea . . . before you figure out what's wrong with it. That feeling was tamped down from the outset with lipid emulsion therapy. I considered the method likely to remain a laboratory phenomenon never to see the clinical light of day, because of the improbability that a clinician with the knowledge and inclination to use it would ever have the opportunity. Amazingly, someone did use it, saved a patient and published the case. Now many people have used it, in fact, and we believe that lipid could be effective in treating a variety of overdoses of (lipophilic) drugs. Fortunately, clinically significant adverse reactions have not been reported. Now, we are faced with a different question: "Can lipid emulsion therapy really be as great as all that? " The two reports in this issue of *Anesthesia and Analgesia* supply part of the answer, "Apparently yes . . . but within limits." Additional, carefully designed laboratory studies and evaluation of clinical reports are needed to get the rest of the answer.

Note added in proof. A recent publication by Mazoit et al. (Mazoit JX, Le Guen R, Beloeil H, Benhamou D. Binding of long-lasting local anesthetics to lipid emulsions. Anesthesiology 2009;110:380–6) indicates that a drop in ambient pH as might occur during asphyxia decreases lipid affinity for both ropivacaine and bupivacaine.

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