Current evidence supports use of lipid rescue therapy in local anaesthetic systemic toxicity

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Conflict of Interest
Dr. Weinberg is founder of ResQ Pharma, Inc. and maintains the educational website, www.lipidrescue.org

doi: 10.1111/aas.12870

Readers may be surprised by the recent editorial of Dr. Rosenberg, 'Current evidence is not in support of lipid rescue therapy in local anaesthetic systemic toxicity'.[1] Lipid rescue therapy (LRT) is widely accepted and recommended for treating local anaesthetic systemic toxicity (LAST)[2] but Dr. Rosenberg purports that the efficacy and safety data are insufficient to warrant its use for this indication. I share his strong preference for evidence-based medicine, including LRT, and the belief that skepticism is a necessary element of applying science to medical practice. However, in reviewing virtually the same clinical and experimental data I draw the opposite conclusion. LRT clearly saves lives and evidence for its efficacy, safety, and mechanism of action are strongest for treatment of LAST. Dr. Rosenberg's arguments fall into three key domains.

Rapid acceptance despite inadequate supportive evidence from the clinic or laboratory

It is useful to remind readers that a decade ago, in the pre-LRT era, LAST was considered dangerously resistant to basic and advanced life support therapy.[3] LRT therefore fills an unmet medical need. The earliest case reports of its use included dramatic, rapid return of vital signs, in many instances after patients had already failed prolonged, standard resuscitative efforts.[4–9] This led to more and earlier use in order to prevent progression to cardiovascular collapse.[10] The subsequent, rapid, and world-wide adoption of LRT reflected the needs of the anesthesia community for an effective treatment of a potentially catastrophic iatrogenic complication where none had been before. While positive publication bias detracts from the utility of case reports for comparing efficacy of various treatments, this does not weaken their value in providing proof of principle: here, that LRT saves lives. The result is that LRT is now typically used soon after onset of LAST so that 'before and after' treatment comparisons in individual case reports are no longer the rule.

Dr. Rosenberg is correct that a randomized controlled clinical trial would be optimal for evaluating LRT for LAST, but he fails to acknowledge that such studies are neither feasible given the rarity of LAST, nor possible for ethical reasons – who would allow their patient, or family member to be randomized to the control group? This problem applies to many effective emergency therapies and the low level of evidence Dr. Rosenberg criticizes in LRT is typical of many treatments used by toxicologists in life-threatening situations.

Experimental data in human and animal models provide clear support for the efficacy of LRT in treating LAST and evidence of superiority to alternatives. The systematic review of animal models cited by Dr. Rosenberg found no

Acta Anaesthesiologica Scandinavica
AN INTERNATIONAL JOURNAL OF ANAESTHESIOLOGY AND INTENSIVE CARE, PAIN AND EMERGENCY MEDICINE

advantage of LRT over vasopressors. However, this study is highly flawed by many critical reporting errors. I am also concerned by their inclusion of pig studies and the failure to address the long-standing question of whether porcine models are even suitable for study of LRT.[11] This is based on the propensity for LRT to provoke in pigs unexplained systemic, cutaneous discoloration, and hemodynamic instability including pulmonary hypertension – indications of serious potential confounders.[12] Dr. Rosenberg also points out that the doses of lipid used in typical animal experiments exceed safe limits for humans. This is simply accounted for by the standard, FDA allometric scaling correction factor (6) for adjusting rat to human doses.

Lack of an accepted mechanism

The argument against LRT that most surprised me is Dr. Rosenberg's contention that the mechanism is simply unknown. First, every practicing anesthesiologist knows this isn't a sine qua non for a treatment's usefulness in our practice – after all, we use inhalational anaesthetics every day. Moreover, a specific, beneficial pharmacokinetic effect is now well described in a variety of LRT models. A volunteer study from Dr. Rosenberg's group showed that lipid infusion reduced bupivacaine context-sensitive half-life from 45 min to 25 min and lowered peak bupivacaine concentration at 20 min by a third compared to controls[13]; another volunteer study from his laboratory showed that lipid infusion reduced non-lipid-entrapped lidocaine area under the concentration curve by 23% over the first 30 min compared to a control infusion.[14] Another volunteer study by Dureau et al. showed that lipid infusion reduced peak local anaesthetic concentrations by 26–30%.[15]

Lipid exerted very similar effects on bupivacaine half-life in a rat study by Shi et al. (beta-half-life shortened by 45%).[16] Fettiplace et al.[17] confirmed in rats that lipid increased the blood : tissue partitioning of bupivacaine and improved cardiac performance. Both rat studies showed that lipid treatment reduced bupivacaine concentrations in brain and heart compared to controls. Thus, four laboratories on three continents report very similar, beneficial pharmacokinetic effects of LRT on local anaesthetic blood concentrations in rats and humans. In sum, LRT accelerates redistribution of bupivacaine, effectively shuttling drug from target organs (brain and heart) to reservoir organs (e.g., liver, skeletal muscle). As stated in Litonius et al., '….the shortening of the bupivacaine context-sensitive half-life caused by lipid emulsion infusion seems to reflect that bupivacaine is distributed into tissues at an increased rate' – an effect seen even at the very low, non-toxic doses of bupivacaine used in their volunteer experiments. In an era of concern about the reproducibility of scientific findings, it is encouraging to know that LRT exerts a consistent, predictable benefit in reducing bupivacaine toxicity across multiple models, methods and laboratories. In fact, very few antidotes have been shown to exert so uniform and reliable an effect as LRT and Dr. Rosenberg's expertise as a superb experimentalist contributed importantly to this body of work. Partitioning is important to LRT but is not the only mechanism. Other relevant, beneficial effects such as post-conditioning,[18] direct inotropy[19] and activation of cyto-protective pathways[20,21] are also reproducible in a variety of models and likely contribute to multimodal effects of LRT that together speed recovery from LAST.

Adverse effects

Clearly the therapeutic index, or ratio of therapeutic to toxic doses, is key to evaluating any potential treatment. The most common adverse effect of LRT is interference with certain laboratory tests. This is not surprising given that lipemia is a goal of LRT. The half-life of hypertriglyceridemia during LRT is 14 min so the effect is short-lived; nevertheless, needed tests can be drawn before LRT and lipemic specimens taken after LRT can be centrifuged to clear the plasma. Therefore, one can argue that this is more correctly viewed as a predictable side effect than a complication. Severe complications related to the use of LRT are rare and directly related to the total dose of lipid delivered, most often reported after oral drug overdose, where LRT may be given for prolonged periods of time. This can potentially lead to the delivery of very large doses (liters) and we have addressed this previously with

recommendations to modify the LRT regimen when prolonged treatment is used.[22] Unfortunately, Dr. Rosenberg failed to distinguish between this scenario and the treatment of LAST, where the total lipid dose delivered is typically on the order of 500 ml. Complications from LRT are exceedingly rare in this setting.

Conclusion

Evidence from the laboratory and clinic strongly indicates that the potential benefit of LRT in preventing morbidity and mortality from LAST far exceeds the potential for causing any harm. Nearly two decades of effort in many laboratories across the globe using human, animal, isolated heart, cell culture, and computational models have established a clear and plausible mechanism for this benefit. Notably, Dr. Rosenberg's work has contributed importantly to advancing the field. I ask readers to re-examine all the data in an entirely objective light (excluding porcine models), then answer the following question, 'Would you use LRT for a patient with LAST'? I think I know the answer.

Note

Fettiplace and McCabe confirm the efficacy of lipid emulsion in a robust meta-analysis of published experimental data from animal models of local anesthetic toxicity.[23]

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