Pediatric Anesthesia

EDITORIAL

Local anesthetic systemic toxicity and animal models for rescue paradigms: can pigs fly?

Mauch and colleagues (1) provide in a recent issue of *Pediatric Anesthesia* an intriguing study of treatment for local anesthetic systemic toxicity (LAST) in piglets receiving sevoflurane anesthesia. Their key finding was that epinephrine administration was the common factor among all the survivors in each of the four treatment groups comprising epinephrine alone, intravenous lipid emulsion (ILE) alone, ILE plus epinephrine, and ILE plus vasopressin. There was no difference in overall survival among the groups. However, only animals receiving epinephrine had initial return of spontaneous circulation (ROSC) and those with delayed ROSC after an initial treatment failure returned only after a second dose of epinephrine. They also noted that among the ILE-treated animals achieving ROSC, lipid appeared to have a 'stabilizing effect' as they required less adrenergic support to maintain circulation. Nevertheless, they concluded that for LAST, '…. epinephrine should be the first-line rescue drug'.

The study by Mauch *et al.* provides an excellent opportunity to share a secret known only to those who have performed such experiments: it is exceedingly difficult to establish an animal model of LAST. Readers looking only for the bottom line of any such study are unlikely to appreciate the gargantuan effort that went into their experiments, starting with formulating a model system that can answer tough questions and provide clinically meaningful insights into a complex biological phenomenon. Our own experience can serve as a canon. We decided several years ago to set up a model of bupivacaine toxicity to compare ILE with other resuscitation methods – much as Mauch has done. We soon realized that every element of the process was fraught with problems. A wrong choice would introduce potential experimental confounders that could limit the relevance of the results or muddy their interpretation. It took the full effort of our laboratory over 10 months and nearly 100 experiments to finalize a system that was highly reproducible and could test hypotheses related to treatment of LAST – all this before collecting any data that would be published (2).

These are some of the key questions to answer first, the 'front load' to such experiments: choice of animal, anesthetic, local anesthetic, its dose, route and rate of administration, treatment protocol(s) and sample size, metrics, endpoints, how to define recovery (e.g., ROSC), and statistical interpretation. Each question might appear uncomplicated, but answering them is rarely straightforward and never simple. Moreover, while simultaneously retaining focus on testing the underlying hypotheses (this is scientific method, after all), one must continually question the clinical relevance of the experiments – that is, 'Will the results influence practice'? One can make an educated guess about each of these elements, but in all likelihood as the pilot experiments progress, the model will be revised many times for practical (e.g., financial), technical, and scientific reasons. Even apparently straightforward questions become very challenging but we will focus on four in this editorial.

First, 'How should we dose the local anesthetic'? If we assume the use of intravenous injection (does this really model clinical LAST?) should a single, defined challenge be administered to all animals or, alternately, should one use an infusion to a chosen physiological endpoint? Which option offers the best chance to test a hypothesis? The first would likely give the most reproducible plasma concentration for animals of a given size range but does not account for interindividual variation in susceptibility to LAST, a very real clinical problem. The later will potentially control for such variation but leaves the experiments open to substantial variation in dose. We tried both methods and opted for the fixed-dose and chose a strain of highly inbred, congenic rats as a means of limiting interindividual variation to the local anesthetic. Mauch *et al.* chose the fixed endpoint. However, the sizable range of doses required (5.1–20.2 $mg \cdot kg^{-1}$ in one group) confirmed substantial interindividual variation in pharmacokinetics or sensitivity to bupivacaine. This becomes more problematic when there are intergroup differences as appears to be the case for groups 1 (epi only) and 2 (lipid only), which received mean doses of 7.7 and 9.0 $mg \cdot kg^{-1}$, respectively. Overall differences among the several groups might have eluded statistical detection, but these doses look different enough to concern me. Were these groups challenged equally? This issue could be particularly problematic since the median plasma concentrations appear different (70 versus 88 microM, groups 1 and 2 respectively). Was this really a fair comparison if the 'winning' treatment was given to the group with the smaller local anesthetic challenge? Moreover, the median plasma bupivacaine levels among surviving animals in these groups (68 and 101 μM, for groups 1 and 2, respectively) also seem sufficiently different to suggest that in these animals, ILE exerted a sink effect, conferred added resistance to bupivacaine, or both. It appears that in avoiding inter-

individual variation in drug response, one accepts the possibility of interanimal and intergroup differences in dose. An identical challenge to each test subject among a population of congenic animals would reduce the contribution of such an important confounder.

Second, 'How should we dose the lipid emulsion'? The authors chose to administer the ILE as a single bolus dose of 4 $ml \cdot kg^{-1}$. Without the benefit of a dose-response trial, how can we know the authors used the right dose of lipid? It is possible that across a range of potential doses, some might be too low, while others too high to allow recovery. Where is the dose used by Mauch *et al*. in this spectrum? The current recommendations for clinical use in humans are 1.5 $ml \cdot kg^{-1}$ by bolus followed by a continuous infusion at 0.25 $ml \cdot kg^{-1}$ per min plus 1–2 repeated boluses for failure of ROSC and increased rate of infusion for sagging blood pressure (3). However, it is unclear how to scale and translate this dosing regimen to a piglet in an experimental model of LAST. This is not a trivial question as the dose and method of delivery are very likely to influence outcome and efficacy. We have noticed over the years that a single bolus in an experimental model of LAST usually does not provide durable recovery. This is in agreement with Mauch's findings. Why didn't they repeat the bolus or follow with a continuous infusion as suggested in the ASRA practice guidelines? Moreover, they did not vary the lipid dose for each animal, although the bupivacaine dose varied from subject to subject. They repeated the epinephrine dose for failure to achieve ROSC, but did not repeat the lipid bolus. Once again, it seems an unfair comparison if additional lipid boluses or a following infusion would have made a difference – we just won't know until those dose-response experiments are reported.

Third, 'How should we dose the epinephrine'? We agree with the authors' approach on this point. Most previous studies of LAST have used much larger doses of epinephrine. For instance, Mayr *et al*. (4) used multiple doses of 45–200 $mcg \cdot kg^{-1}$ of epinephrine in combination with repeated doses of 0.4–0.8 $U \cdot kg^{-1}$ of vasopressin to treat bupivacaine overdose in pigs. Similarly, Hicks *et al*. (5) used high doses of epinephrine (100 $mcg \cdot kg^{-1}$) plus vasopressin for 10 min following bupivacaine challenge and prior to randomization into treatment groups (saline vs ILE). We believe that such dosing is not readily scalable to humans, and given that doses above 10 $\mu g \cdot kg^{-1}$ epinephrine might impair the efficacy of ILE (6), we do not consider it wise to use high-dose epinephrine in clinical LAST and suggest using doses less than 1 $mcg \cdot kg^{-1}$. This is reflected in the recent ASRA guidelines for treating LAST. Mauch *et al*. show in their model a clear benefit to using epinephrine which we attribute to their use of modest doses. Furthermore, they reduced the dose of epinephrine when the MAP was low, but beyond their ROSC threshold, titrating the dose to a physiologic endpoint. Physicians and their patients will benefit when this judicious approach is translated to the clinic.

Finally, another important observation requires us to ask 'Is the pig an acceptable model of LAST'? Niiya *et al*. (7) recently noted that ILE in pigs can provoke rapid onset of generalized cutaneous mottling with red discoloration. We wonder whether this could be similar to the well-described phenomenon of complement activation-related pseudoallergy or CARPA that reproducibly occurs in pigs after infusion of certain liposome formulations (8). Rats are relatively resistant to CARPA (9), and this species-specificity might result from differences in lipid particle processing that occurs by pulmonary intravascular macrophages (PIM) in the pig and in hepatic Kupffer cells in rats and humans. PIMs release cytokines in response to activation by the liposomes, causing pulmonary hypertension (a predictable effect of CARPA) and, potentially, cardiovascular instability and collapse. Pigs have long been a gold standard for the study of resuscitation. However, if they are hypersensitive to ILE, pigs might not be Kosher for studies of lipid resuscitation. Further investigation of this concern is warranted.

It should be clear that establishing laboratory models to study LAST is not for the feint of heart. Despite our concerns about their model, we acknowledge the efforts of Mauch *et al*. in contributing to the literature on this topic. We interpret their findings to suggest that epinephrine in small doses could aid in resuscitation from LAST. However, other laboratory studies and many clinical reports indicate that ILE can facilitate resuscitation from local anesthetic-induced cardiovascular instability (10), even when standard (i.e., pressor) therapy has failed (11). We have reviewed a few of the reasons that caution must be exercised in extrapolating from the findings of a particular animal model of LAST treatment to the clinical setting. The authors are to be recognized for joining the daunting search for the ideal treatment of LAST. The answer awaits.

Guy Weinberg[1] & Santhanam Suresh[2]
[1]*Professor of Anesthesiology and the Department of Anesthesiology, Jesse Brown VA Medical Center, University of Illinois, Chicago, IL, USA*
[2]*Professor of Anesthesiology & Pediatrics, Children's Memorial Hospital, Northwestern University's Feinberg School of Medicine, Chicago, IL, USA*
Email: ssuresh@childrensmemorial.org

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