

Lipid Reversal of Bupivacaine Toxicity: Has the Silver Bullet Been Identified?

Since the first reports of unexpectedly difficult resuscitations after accidental intravenous administration of bupivacaine or other long-acting local anesthetics (LA), investigators have pursued 2 divergent lines of research.¹ One line of investigation, attempting to define the mechanism for local anesthetic-induced cardiac arrest, has focused on differences between longer-acting (e.g., bupivacaine) and shorter-acting (e.g., lidocaine) LA.²⁻⁵ A variety of potential mechanisms have been considered. Many have concentrated on electrophysiologic actions of LA, and in particular, drug actions on cardiac sodium and calcium channels. Others have focused on the negative inotropic actions of LA emphasizing LA-mediated alterations in mitochondrial bioenergetics and intracellular calcium processing. LA are well recognized to produce toxic reactions in the central nervous system, and some investigators have even linked increased local anesthetic concentrations within the brain with dysrhythmias. Finally, investigators have noted that bupivacaine interferes with intracellular signaling and have questioned whether resuscitation difficulties might relate to local anesthetic interactions with the actions of resuscitation drugs.

The other line of investigation generally has assumed either an electrophysiologic or contractile mechanism of cardiac toxicity, then has focused on identifying the best agent or technique by which to salvage the unfortunate patient or experimental animal subjected to local anesthetic intoxication.⁵ Thus, a long series of drugs that serve either as antiarrhythmics (phenytoin, bretylium, and many others), positive inotropics (isoproterenol, epinephrine, amrinone, insulin, and others), or vasopressors (epinephrine, vasopressin) and even extracorporeal circulation have been considered. In this cardiac-oriented mix we now find, to our surprise, an intravenous lipid emulsion.^{6,7} Yes, this is the same lipid that has been used for years as a part of parenteral nutrition and as a vehicle for the general anesthetic propofol. Weinberg et al. present in this issue of *RAPM* their provocative results that a bolus dose of lipid can reverse an animal model of bupivacaine cardiac toxicity after standard resuscitation has failed. Although this work cannot define a mechanism for these surprising findings, it seems likely that in some way the lipid is serving to more rapidly remove local anesthetic molecules from whatever binding site serves to produce the cardiovascular depression that has come to be known as bupivacaine toxicity. It may also be possible that the lipid is inducing some sort of metabolic change in the heart that serves to overcome bupivacaine intoxication.

Three questions emerge from this work. First, should clinicians treat bupivacaine overdosage with lipid bolus emulsion? Second, given that lipid emulsion is likely not to be readily available at anesthetizing sites, should bupivacaine toxic side effects be treated with bolus propofol, which is formulated with lipid? Third, does the use of infused propofol (and the lipid with which it is formulated) result in protection from local anesthetic-induced toxicity?

Our answer to the first question is an unqualified YES, but only after other, more conventional treatments have proven unsatisfactory. It clearly does not make sense at this time to treat local anesthetic-induced tremors or seizures with

lipid as a first response. Clinicians should focus on airway management (and protection in the case of patients with full stomachs), oxygenation, ventilation, and protecting the patient from injury. When the central nervous system (CNS) hyperactivity does not cease spontaneously, small doses of barbiturate, benzodiazepine, or even propofol may be used.⁸ One problem with propofol is its possible association with “seizure-like phenomena.”⁹ The need for paralysis and intubation will depend on the circumstances. In any case, such CNS toxicity is usually short-lived. By the time lipid might be available for infusion, the CNS toxicity will be over, and in any case, the available data are contradictory as to whether lipid is effective for this.¹⁰ In the case of cardiac arrest, we recommend that standard guidelines for Advanced Cardiac Life Support (ACLS) be followed. Thus, following prompt electrical defibrillatory attempts, coronary perfusion should be supported using either epinephrine or vasopressin (we much favor the latter due to our strong suspicion that it will less likely be associated with drug-induced ventricular fibrillation and may lead to less acidosis).¹¹ Similarly, we would favor the use of amiodarone over lidocaine due to our aversion to administering more local anesthetic to patients already suffering from local anesthetic toxicity.¹² Nevertheless, given that local anesthetic cardiac toxicity may be so difficult to treat and given the well-known safety profile of lipid infusions, we would initiate intravenous lipid infusion at the earliest sign of severe local anesthetic-induced cardiac toxicity.

Our response to the second question is simple: we would use propofol to treat local anesthetic-induced cardiac arrest only after all other conventional (ACLS) treatments had proven unsuccessful, and *only* if lipid infusion (without the active di-isopropylphenol anesthetic) were not available. One concern is that human resuscitation is not the proper time to first test hypotheses regarding drug actions. Animal experimentation should precede human experimentation whenever possible. Likewise, the use of propofol as an “antidote” to local anesthetic cardiotoxicity should proceed with caution, because its well-known negative inotropic properties may further exacerbate cardiac depression from the local anesthetic.

The third and final question is tantalizing. It may be true that the choice to infuse sedation doses of propofol rather than benzodiazepines or other agents during surgery under regional anesthesia will reduce the susceptibility to local anesthetic-induced toxicity, due to the obligatory lipid load. However, previous studies suggest that local anesthetic-induced seizures respond to propofol, not to lipid.¹⁰

Weinberg’s findings are striking, and we hope that other investigators will soon confirm and extend them. We look forward to reading the results of such additional studies and hope that they will transform our approach to local anesthetic toxic reactions.

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