Chapter 15
Management of Local Anesthetic Systemic Toxicity (LAST)

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A 70 kg otherwise healthy 32-year-old G4P0 at 22 weeks of gestation who is status post a motor vehicle accident with multiple rib fractures, L2 and L3 burst fractures, and an open right distal tibia and fibular fracture is scheduled for an open reduction and internal fixation of her right leg. The patient is very worried about general anesthesia given her prior miscarriages. Because of her strong preference for regional anesthesia and concern with performing a neuraxial anesthetic immediately after spinal trauma, peripheral nerve blocks were chosen as the anesthetic plan. Ultrasound-guided femoral and sciatic nerve blocks were performed using 25 cc of 2% lidocaine with epinephrine for the femoral and 20 cc of 2% lidocaine with epinephrine for the sciatic done in the popliteal fossa.

Approximately 10 min after the second block is completed, the patient becomes very anxious, and she complains that her tongue and lips are tingling (L1–22).

L-1. What Are the Symptoms of LAST, and How Do They Correlate with Plasma Concentrations?

Older studies suggest a biphasic sequence of symptoms for both central nervous system (CNS) and cardiovascular system (CVS) toxicity. Typically, there is CNS stimulation followed by depression and CVS stimulation followed by collapse (Fig. 15.1).

This relationship is based on data from volunteers who were given infusions of local anesthetics and monitored for symptoms [1, 2]. Five volunteers got infusions of intravenous bupivacaine at 10 mg/min until 125 mg was given or symptoms were severe enough to stop the infusion. One week later, they received lidocaine at 20 mg/min until 250 mg was given. This was compared to symptoms using etidocaine.

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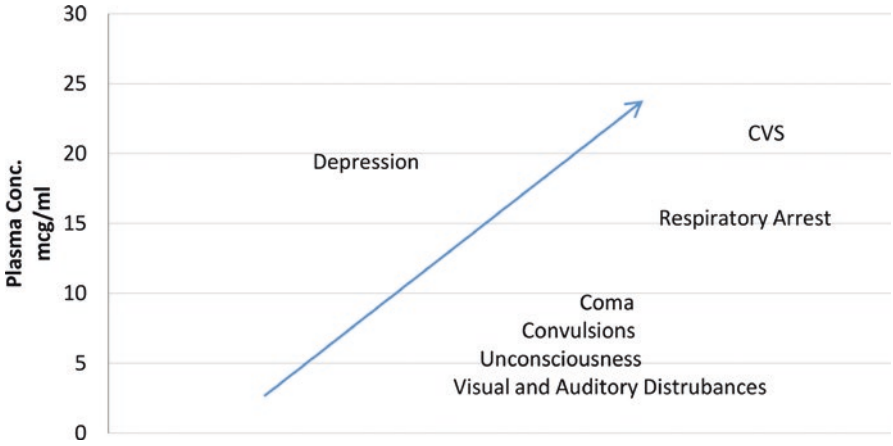

Fig. 15.1 Relationship of signs and symptoms of local anesthetic toxicity to plasma concentrations of lidocaine. (Based on data from Refs. [1, 2])

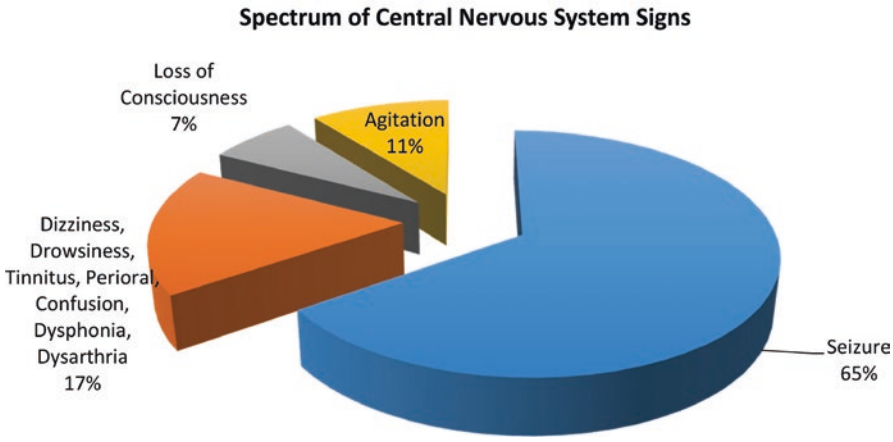

Fig. 15.2 The range of presenting CNS symptoms in confirmed cases of LAST. (Adapted from Di Gregorio et al. [3]. With permission from Wolters Kluwer Health, Inc.) [5]

The first finding is the local effect on the tongue and mouth from the local anesthetic (LA) leaving the vascular space and anesthetizing the nerve endings causing tongue or perioral numbness. Following this, neuroexcitatory symptoms were seen due to blocking inhibitory pathways followed by neurodepression due to blockage of inhibitory and facilitatory pathway. CVS effects have a similar excitatory effect with hypertension and tachycardia, followed by myocardial depression and decreased cardiac output.

In situations where large doses or rapid injections are given, this gradual progression of symptoms is less likely as evidenced by more recent data describing the presenting symptoms in known LAST cases (see Figs. 15.2 and 15.3) [3]. Rather than seeing the gradual onset of symptoms described in the controlled setting, patients may present with symptoms such as seizure loss of consciousness [4].

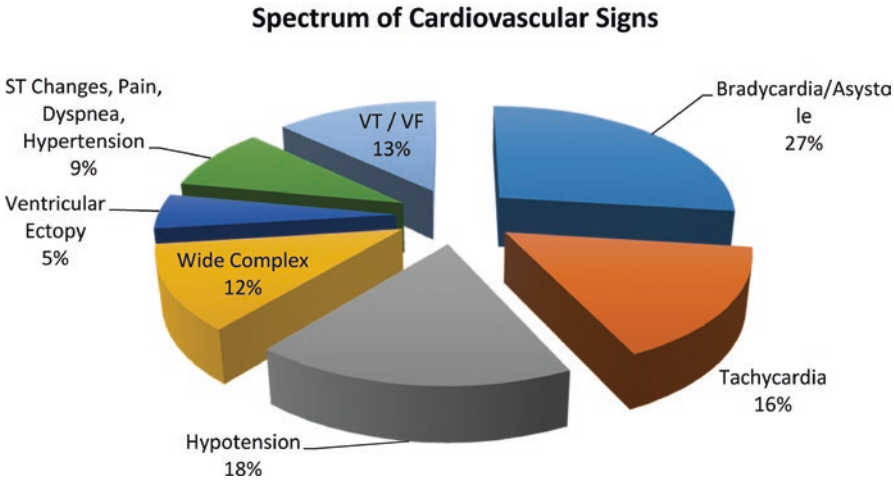

Fig. 15.3 Spectrum of presenting cardiovascular symptoms in confirmed cases of LAST. (Adapted from Di Gregorio et al. [3]. With permission from Wolters Kluwer Health, Inc.) [5]

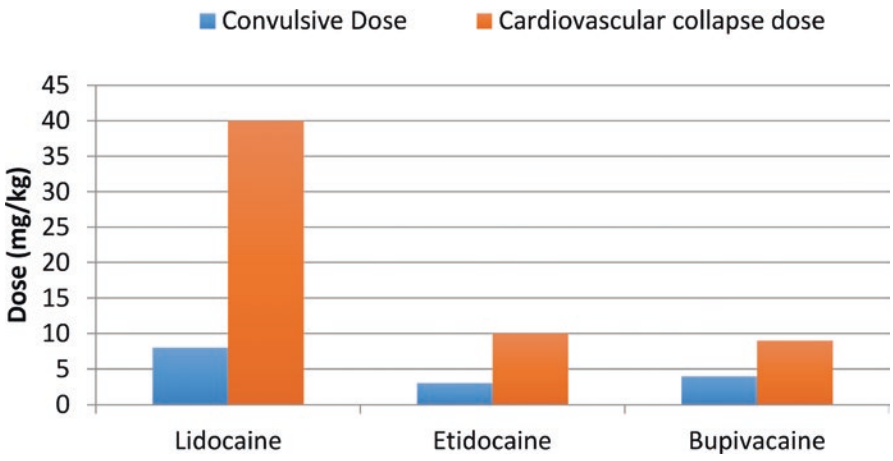

Fig. 15.4 Relative toxic doses to cause convulsions versus cardiovascular collapse of three different local anesthetics. (Reprinted from Rogers et al. [7]. With permission from Elsevier)

L-2. In the Presence of CNS Symptoms with Lidocaine, What Is the Likelihood of Impending Cardiac Instability?

The likelihood of CVS instability from LAST depends on the local anesthetic used. With lidocaine, the dose at which CVS symptoms are seen is approximately four times the dose required to generate CNS symptoms. For the more potent lipophilic local anesthetics like bupivacaine, the dose to generate CVS collapse is much closer to the one required for CNS toxicity and convulsions (see Fig. 15.4) [6].

L-3. If There Is CV Instability with Lidocaine, What Is the Likelihood of a Successful Resuscitation?

The rate of successful resuscitation in dogs after cardiovascular collapse from intravenous infusions of lidocaine, bupivacaine, levobupivacaine, and ropivacaine was evaluated [8, 9]. Success rates (see Fig. 15.5) were greater for resuscitations from lidocaine (100%), than ropivacaine (90%), than levobupivacaine (70%), and than bupivacaine (50%). Required doses to induce cardiovascular collapse were greater for lidocaine (127 mg/kg), than ropivacaine (42 mg/kg), than levobupivacaine (27 mg/kg), and than bupivacaine (22 mg/kg). From this data we can see that the dose required to generate CVS toxicity from lidocaine is extremely high, and if it were to occur, the likelihood of a successful resuscitation is also high.

L-4. Your Colleague Suggests Giving Lipid Emulsion, How Does Lipid Emulsion Work?

The understanding of the mechanism for how a lipid emulsion works for LAST has evolved from a static lipid sink and metabolic substrate hypothesis [10] to one that involves dynamic shuttling, hemodynamic, and postconditioning effects [11]. The lipid shuttle allows for local anesthetics to be transferred from highly vascular organs like the brain and heart that are sensitive to local anesthetics to the muscle and liver for storage and metabolism. The metabolic mechanism suggests that the lipid emulsion provides the fatty acid substrate required from ATP generation by the mitochondria. The theory is based on the fact that local anesthetics inhibit carnitine-acylcarnitine translocase (CAT). CAT is the intracellular enzyme responsible for the transfer of long-chain fatty acids into mitochondria for ATP production (see Fig. 15.6). The theory is that the enzymatic inhibition by local anesthetics is overwhelmed by the massive amounts of fatty acids allowing ATP production to resume. This is supported by evidence from a patient with carnitine deficiency who was particularly sensitive to developing arrhythmias with low-dose bupivacaine. Additionally, lipid emulsion improves contractility in a rat model of LAST and a canine model of myocardial stunning. Additionally, lipid has been shown

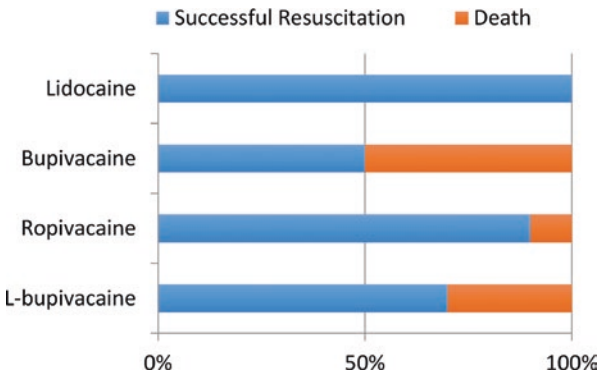

Fig. 15.5 Likelihood of death vs. successful resuscitation after various local anesthetics in dogs. (Based on data from Refs. [9, 10])

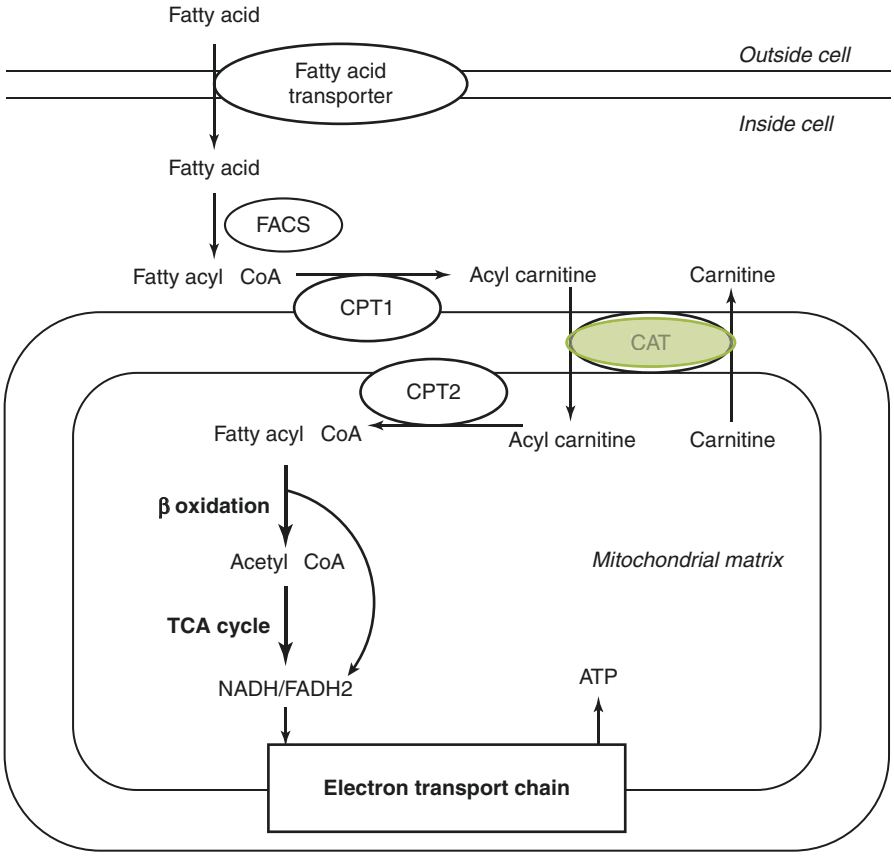

Fig. 15.6 The steps required for a fatty acid to get into the mitochondria and be utilized to generate ATP via the electron transport chain. *FACS* fatty acyl CoA synthetase, *CPT1* carnitine palmitoyltransferase 1, *CPT 2* carnitine palmitoyltransferase 2, *CAT* carnitine acyltransferase, *TCA* the citric acid cycle

to reduce myocardial ischemia-reperfusion injury and may also be acting in this way during treatment of LAST. Using mathematical computer modeling, the need for the additional factors impacting recorvery were identified. The beneficial effects of lipid infusion via volume expansion and improved cardiac performance help satisfy the model [11].

L-5. What Physiochemical Property of the Local Anesthetic Will Predict the Utility of Lipid Emulsion in LAST?

Lipid solubility is the primary determinant of a local anesthetic getting absorbed by an infusion of lipid emulsion. Lipid solubility is secondary to the carbon groups on the benzene ring (see Fig. 15.7). The more lipid soluble a local anesthetic is, the

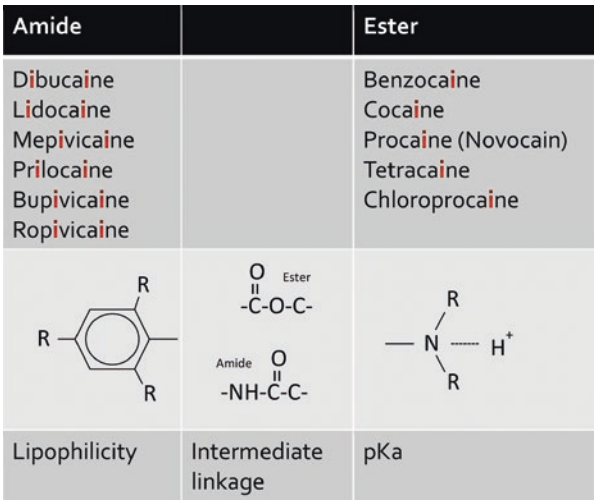

Fig. 15.7 Comparison of amide and ester local anesthetics. The chemical structure of the local anesthetics determines its class (amide or ester) and its physiochemical properties like lipophilicity and pKa. The lipophilicity comes from the benzene ring at one end, and the pKa is related to the amine group at the other

Table 15.1 Table of chemical properties of various local anesthetics

	pKa	% unionized @ pH 7.4	Onset (fast or slow)	Typical conc (%)	Lipid solubility	Protein binding (%)
Mepivacaine	7.7	33	Fast	1.5	130	77
Lidocaine	7.8	28	Fast	1	366	64
Ropivacaine	8.1	17	Slow	0.5	775	94
Bupivacaine	8.1	17	Slow	0.25	3420	95
Tetracaine	8.4	9	Slow	0.2	5822	93

As lipid solubility increases reflecting an increase in potency, the concentrations needed in clinical use decrease

more easily it can cross through a neural membrane allowing it to be more potent. This is reflected by more lipid-soluble local anesthetics being used at lower concentrations than the less potent ones. See Table 15.1 for relative lipid solubilities measured in octanol/water binding coefficients.

L-6. What Is the Likelihood That Lipid Emulsion Will Work on Less Lipid-Soluble Local Anesthetics?

In vitro studies have revealed that local anesthetics will inhibit the flow of a current across a membrane by inhibiting a voltage-gated proton pumps. When exposed to lipid emulsion, this effect is blocked for bupivacaine but not significantly for lidocaine [12]. Similarly, when rat hearts were pretreated with lipid emulsion (0.25 ml/kg/min × 10 min) prior to the administration of bupivacaine, the onset of asystole was delayed. No such beneficial effects were seen in preventing mepivacaine-induced cardiotoxicity, and the recovery period was prolonged in the rats that got

lipid emulsion [13]. This would suggest that lipid emulsion was actually detrimental to the resuscitative efforts from mepivacaine.

Furthermore an earlier study from the same group showed that lipid emulsion hastens the electrical and hemodynamic recovery of isolated rat hearts from bupivacaine but not for ropivacaine or mepivacaine [14]. Despite the lack of experimental evidence supporting the use of lipid emulsion for the resuscitation from less lipophilic local anesthetics and animal data to suggest potential for harm, there are several case reports and anecdotes on the lipidrescue.org supporting its success and encouraging its use.

L-7. Despite the Lack of Evidence Supporting Lipid Emulsion Therapy in the Context of Lidocaine Toxicity, Are There Any Risks of Giving Lipid Emulsion to the Mother?

There have been no reported adverse effects from giving lipid emulsion for clinical treatment of LAST. Most risks associated with lipid emulsion are from long-term use except anaphylaxis, which can occur acutely [15, 16]. In rats, the LD50 for lipid emulsion was 68 ml/kg which was approximately three times the therapeutic dose [17]. The plasma triglycerides were noted to be elevated for less than 48 h, and there was a subsequent increase in amylase 1816–2804 U/L (40–140 U/L) and AST 45–284 U/L (8–35 U/L). The histologic appearance of the brain, heart, pancreas, and kidneys was all normal. The lung had thickening of the alveolar septae and a few intra-alveolar foamy histiocytes at 60 ml/kg and hemorrhagic vascular congestion at 80 ml/kg. There was also a dose-related finding of hepatic microvascular steatosis with extensive necrosis at the highest dose.

It has been suggested that other possible consequences of high-dose lipid emulsion may be extrapolated from findings associated with the use of lipid infusion for nutrition [16]. Of note, the typical duration of exposure is much longer when used for nutritional purposes than for toxicity treatment, but the peak dosing is less. For example, the dosing for infants who had received TPN and had histopathologic evidence of pulmonary fat embolism is shown in Table 15.2 [19].

Table 15.2 Patient data for cases of pulmonary fat embolism after infusion of lipid emulsion [18]

	Case 1	Case 2	Case 3	Case 4
Body weight (kg)	1.65	1.48	2.76	3.13
Mean rate (ml/kg/h)	0.7	0.75	0.4	0.6
Max rate (ml/kg/h)	0.9	1.05	2.55	3.5
Total duration (days)	11	14	12	18

Adapted from Barson et al. [19]. With permission from BMJ Publishing Group Ltd
The max hourly rate given to the infants is less than the max dose recommended for the first 30 min in LAST of 10 ml/kg, but the cumulative dose given over the course of several days far exceeds the LAST doses

Another consideration when giving a large dose of lipid emulsion is allergic reaction. Lipid emulsion contains soybean oil 20% = 200 mg/ml (long-chain triglycerides), egg yolk-derived phosphatides 12 mg/ml, and glycerin 22 mg/ml. Phosphatides serve the purpose of emulsification or mixing of two immiscible materials. The phosphatide in lipid emulsion comes from egg lecithin. Typically, allergic individuals are sensitive to the glycoproteins in soy or egg white albumin and not to the lecithin. Regardless, there is a theoretical risk of protein contamination in the lipid and subsequent allergic reaction in a sensitive individual.

L-8. What Factors Affect Whether Local Anesthetics Will Cross the Placenta?

Local anesthetics cross the placenta by simple diffusion, not active transport or pinocytosis. The factors that affect how much crosses are protein binding, lipid solubility, maternal plasma concentration, maternal pH, and fetal pH [18]. At equilibrium the fetal/maternal ratio is approximately 0.3 for bupivacaine and 0.6 for lidocaine. However, the lower fetal concentrations of plasma proteins like **α**1 acid glycoprotein cause a higher fetal free fraction of drug and a similar concentration of drug capable of causing toxicity [20]. In the context of fetal acidosis, ion trapping can take place through protonation of the local anesthetic making it unable to diffuse back to the maternal circulation and eventual accumulation on the fetal side [21].

L-9. Are There Any Risks to the Fetus in Utero by Giving the Mother Lipid Emulsion?

Triglycerides are too large to cross the placenta and are broken down by the placenta into fatty acids, which do cross. There is currently only one report in the literature of giving lipid emulsion for LAST in pregnancy, and it worked effectively without any known negative effects [22]. That case was an 18-year-old G1P0, 86 kg at 38 weeks of gestation for induction of labor. The patient's blood pressure (BP) was 160/81 mmHg, and she had mild proteinuria with occasional fetal heart rate (FHR) decelerations. An epidural was placed, and negative test dose of 4 cc 2% lidocaine was administered. Six milliliters of 0.25% bupivacaine was given with good pain relief. Over the next 15 min, the BP increased to 172/114 mmHg and HR 86 bpm with pronounced FHR decelerations. After negative aspiration, 100 mcg fentanyl +10 cc of 0.5% bupivacaine is given via epidural in preparation for cesarean section (CS). Following injection the patient became restless and agitated and then began twitching and became unresponsive. Aspiration of catheter at that time was clearly positive for blood. At that time, two 50 cc boluses of 20% lipid emulsion were given, and the patient regained full consciousness, but there was ongoing fetal

bradycardia. An emergency CS was performed under general anesthesia resulting in a delivery of a 6 lbs infant with APGAR scores of 0^{1}, 7^{5}, and 10^{10}. Both mother and baby were discharged home on POD#4 without complication.

With only one case report of its use in pregnancy, the potential fetal risks could be extrapolated from data on the use of total parenteral nutrition (TPN) in pregnancy [23]. TPN also contains 10–20% lipid solutions and has been evaluated in malnourished pregnant women who required TPN for a range of 14–220 days. In the study group of 26 women all with conditions significant enough to require TPN, 7 were delivered preterm without congenital malformations, and 1 psychiatric patient with diabetes who developed a hyperglycemic coma resulted in an intrauterine fetal demise (IUFD). In all patients there was ultrasound evidence of improved fetal growth after starting TPN [24].

In another study looking at the effect of TPN on the placenta in 20 women, all but one had a normal placenta. That patient received TPN for 8 weeks and had placental fat deposits noted prior to a 22 week IUFD [25].

There is data from the pediatric literature that administration of lipid emulsion to a newborn can result in pulmonary lipid emboli [26] and potentially an increase in pulmonary vascular resistance [27].

L-10. To Prevent the Progression of the CNS Symptoms to a Seizure, What Are the Options for Treatment?

The best option for treatment of LAST-induced seizure is midazolam. In the absence of immediate access to midazolam, propofol could be used while carefully considering its potential impact on the blood pressure. Please note, propofol can**not** be used as a lipid sink in place of a lipid emulsion. It contains 10% lipid so to give the equivalent amount of lipid as is recommended for the initial bolus to treat LAST (1.5 ml/kg of 20% lipid emulsion), one would be giving 200 ml of propofol at once (ten 20 ml syringes).

L-11. Why Is Prevention of a Seizure Important?

There can be rapid development of hypoxia and respiratory and metabolic acidosis during immediately after a seizure [28]. A clinical report of two cases of seizures from LAST where rapid blood gas values were obtained was published by Moore et al. [29]. In the first patient, 3 min after the first seizure, the blood gas was 7.09/59/33/17 (pH/pCO_2(mmHg)/PO_2(mmHg)/HCO_3(mEq/L). In the other patient, 1 min after the onset of the seizure, the blood gas was 6.99/76/87/17 (pH/pCO_2(mmHg)/PO_2(mmHg)/HCO_3(mEq/L). Between convulsions, attempts at ventilating both patients with 100% O_2 were being made.

These rapid rises in CO_2 are significantly faster than what had been reported in apneic awake or anesthetized patients where the expected rate of rise in the CO_2 is 13 mmHg in the first min and 6 mmHg/min after that [30].

L-12. What Effect Does Acidosis Have on Local Anesthetics?

Local anesthetics are weak bases and cross the lipid bilayer in the uncharged form (see Fig. 15.8). Once intracellular, they can become protonated depending on their pKa relative to the surrounding pH. Once protonated, they bind the intracellular portion of the Na channel to prevent depolarization and signal conduction along the nerve.

In the context of acidosis, the local anesthetics may be less likely to cross the membrane, but the ones that have will stay protonated and bound to the sodium channel.

L-13. Resuscitation Guidelines for LAST Emphasize the Primacy of Oxygenation and Ventilation. Is There Evidence to Support that Hypoxia and Acidosis Is Especially Harmful in the Recovery from LAST?

A study that sheds light on this took ewes, performed a tracheostomy, and invasively monitored electrocardiograms, encephaloelectrogram, and arterial pressure [31].

They then received either lidocaine at low (5.7 mg/kg) or high doses (11.4 mg/kg) or bupivacaine at low (2.1 mg/kg) or high doses (4.2 mg/kg).

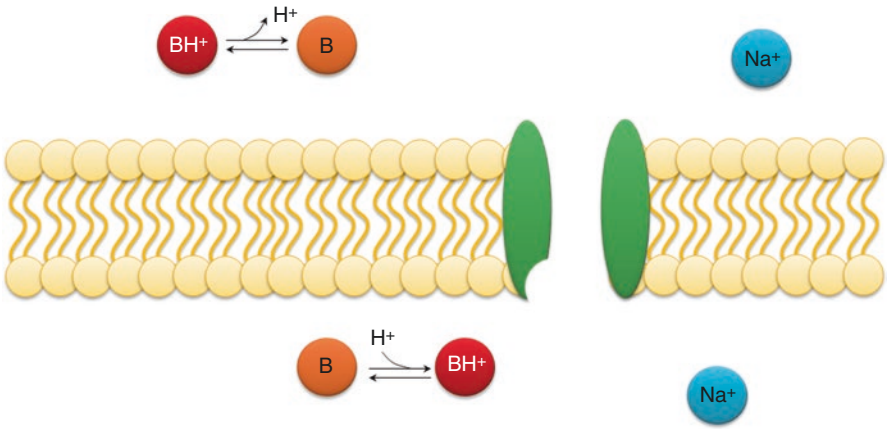

Fig. 15.8 Steps required for a local anesthetic (B) to give up a proton (H+) and cross the lipid bilayer to get the site of action at the intracellular portion of the sodium channel

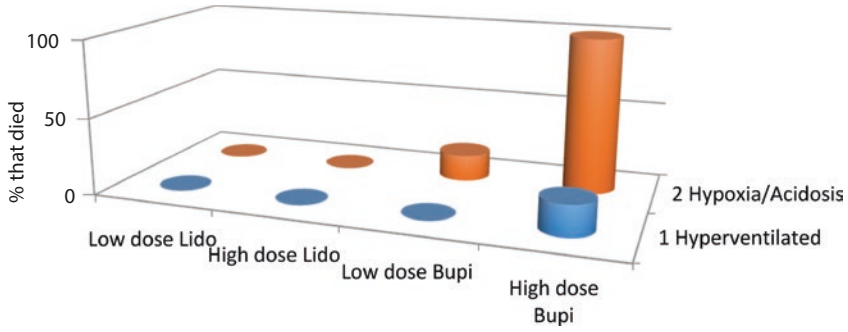

Fig. 15.9 Survival rates of sheep after LAST in the context of the sheep that spontaneously hyperventilated vs. the ones with induced hypoxia (PO_2 50 mmHg) and acidosis (pH 7.15 and CO_2 85 mmHg). (Based on data from Refs. [31, 32])

Their findings showed that the ewes spontaneously hyperventilated during a LAST-induced seizure and maintained pH > 7.35 and all survived. In a subsequent study, the investigators induced hypoxia and a respiratory acidosis by ventilating with CO_2 until the pH was 7.15, the PO_2 was 50 mmHg, and the CO_2 was 85 mmHg. They then administered one of the four local anesthetic regimens listed above [32].

In contrast to the hyperventilating sheep, they found that all of the acidotic and hypoxic ones in high-dose bupivacaine group died (see Fig. 15.9).

L-14. For This Patient, Who Got Lidocaine Alone and Showed Early Signs of CNS Toxicity, Would You Give Any Medications to Treat Her?

The priorities in management are first to ensure oxygenation and ventilation and second to prevent the seizure. Given the potential for cardiac depression from propofol, midazolam would be a preferable option for treating seizures from LAST. If midazolam was not immediately available, judicious use of propofol would also be a reasonable option.

L-15. Take the Same Scenario, and Let's Assume She Got Her Peripheral Nerve Injections with 0.5% Bupivacaine (Instead of Lidocaine) and She Developed the Same CNS Symptoms. Would You Treat? With What?

In the presence of neurological symptoms from a lipid-soluble local anesthetic that causes cardiotoxicity and CNS toxicity at similar doses, it would be appropriate to move rapidly to lipid emulsion to prevent the progression of symptoms.

L-16. What Is the Evidence that Lipid Emulsion Works?

The initial report by Dr. Guy Weinberg in 1998 described an incidental discovery that a lipid infusion significantly increased the LD50 of bupivacaine in rats [33]. Subsequently, the findings have been confirmed in other animal models and supported by multiple clinical reports of its use during resuscitation from LAST and other lipid-soluble drug overdoses. As a result, it has been adopted into the resuscitation guidelines by multiple professional societies including the American Society for Regional Anesthesia guidelines published in 2010 with revisions in 2012 and 2018. This widespread acceptance has preceded full understanding of the mechanism of action(s) or its specific indications. The rapid expansion of its use has been hastened from additional research from Dr. Weinberg's group and others cautioning against the use of what would otherwise be the drugs of choice during resuscitation like epinephrine and vasopressin.

L-17. What Is the Dose of Lipid Emulsion?

The dose of 20% lipid emulsion is as follows for a patient below 70 kg: First, bolus 1.5 ml/kg over 2–3 min, and then repeat after 5 min. Second, infuse 0.25 mg/kg/min or 15 ml/kg/h. Third, stop infusion after CVS stability has been present for more than 10 min. Fourth, keep dose less than 10 ml/kg in the first 30 min. For a patient above 70 kg: First, bolus 100 mL over 2–3 min. Second, infuse 200–250 mL over 15–20 min.

L-18. This Patient Was Supposed to Go Home After Their Procedure, Would You Still Send Them Home? Would You Still Do the Procedure?

The recommendation from the Checklist for Treatment of LAST [34] is to monitor for at least 4–6 h after a cardiovascular event or at least 2 hours after an isolated neurological event. The decision to proceed with the case should be based on the severity of the reaction and the magnitude of treatment that was required. If there was accompanying hemodynamic instability, it seems prudent to avoid further complicating the situation by proceeding with surgery.

L-19. Is Using a Checklist Effective?

Trainees who used the ASRA checklist for management of LAST were twice as likely to complete medical management steps correctly [35]. Of note, of the trainees using the checklist, 40% only partially used it. It is recommended to have a copy of a LAST treatment along with lipid emulsion immediately available in any area where local anesthetics are given in significant doses.

L-20. Can We Follow Standard ACLS Protocols? What Aspects Are the Same/Different?

As with ACLS, the LAST management algorithm starts with airway management with the goal of avoiding hypoxia and acidosis. There are subsequent steps and considerations that deviate from standard ACLS and are unique to the management of LAST (Table 15.3).

Table 15.3 Recommendations for treatment of LAST

If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia, hypercapnia, and acidosis, which are known to potentiate LAST. (I; B)
Lipid emulsion therapy *(I; B):*
Administer at the first signs of LAST, after airway management
Timeliness of lipid emulsion is more important than the order of administration modality (bolus vs. *infusion)*
20% lipid emulsion BOLUS
100 mL over 2–3 min if patient is over 70 kg
1.5 mL/kg over 2–3 min if patient is less than 70 kg
20% lipid emulsion INFUSION
200–250 mL over 15–20 min if patient is over 70 kg
0.25 mL/kg/min if patient is less than 70 kg (ideal body weight)
If circulatory stability is not attained, consider rebolus or increasing infusion to 0.5 mL/kg/min
Continue infusion for at least 10 min after circulatory stability is attained
Approximately, *12 mL/kg* lipid emulsion is recommended as the upper limit for initial dosing *(IIb; B)*
Propofol is not a substitute for lipid emulsion (*III. B*)
Seizure control:
If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, *lipid emulsion* or small doses of propofol are acceptable (I; B)
Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of cardiovascular compromise (III; B)
If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia (I; C)
If cardiac arrest occurs:
If epinephrine is used, small initial doses (≤1 μg/kg) are preferred (*IIa: B*)
Vasopressin is not recommended (III; B)
Avoid calcium channel blockers and β-adrenergic receptor blockers (III; C)
If ventricular arrhythmias develop, amiodarone is preferred (IIa: B): treatment with local anesthetics (lidocaine or procainamide) is not recommended (III: *B*)
Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of CPB (*I*; *B*). Because there can be considerable lag in beginning CPB, it is reasonable to notify the closest facility capable of providing it when cardiovascular compromise is first identified during an episode of LAST

(continued)

Table 15.3 (continued)

Patients with a significant CV event should be monitored for at least 4–6 h. If the event is limited to CNS symptoms that resolve quickly, they should be monitored for at least 2 h (IIa; B)
Use written or electronic checklists as cognitive aids during the management of LAST. A dedicated reader improves adherence to the checklist (I; A)

These recommendations are intended to encourage optimal patient care but cannot ensure the avoidance of adverse outcomes. As with any practice advisory recommendation, these are subject to revision as knowledge advances regarding specific complications
The class of recommendation and level of evidence for each intervention are given in parenthesis (see Table 1)
Changes from the 2010 LAST practice advisory [42] are italicized
CPB indicates cardiopulmonary bypass

L-21. Why Is the Dose of Epinephrine Reduced?

This is based primarily on animal studies that revealed that lower doses of epinephrine (1–2 mcg/kg) were associated with better metabolic and hemodynamic profiles after resuscitation from LAST than higher doses (10–25 mcg/kg) [36].

Lower doses of epinephrine resulted in a return of spontaneous circulation (ROSC) faster than with saline and allowed for maintenance of hemodynamics stability without the decompensation that was seen with higher doses of epinephrine.

It should be noted the studies that showed higher doses of epinephrine to be detrimental, gave a single high dose, and did not give subsequent vasopressors to support the hemodynamics. Also of note, there is animal data to show that in the context of hypoxia or compromised coronary perfusion and LAST, epinephrine is superior to lipid for resuscitation [38, 39].

L-22. Why Is Vasopressin Discouraged in Context of LAST?

In animal studies evaluating the use of vasopressors in resuscitation from LAST (20 mg/kg of bupivacaine), rats that got vasopressin (0.4 U/kg) or vasopressin and epinephrine (30 mcg/kg) developed "red-tinged" pulmonary edema and had a measurable increase in their wet/dry lung weight ratios [40]. Also of note, the resuscitations were less successful from a metabolic and hemodynamic perspective when compared to lipid emulsion alone. As a result, the resuscitation guidelines caution against its use because of these worse outcomes and the association with "pulmonary hemorrhage." In the paper that is referenced, however, the diagnosis of pulmonary hemorrhage is never used, but rather, the mice that received vasopressin were noted to have red-tinged pulmonary edema fluid in the expiratory limb of the breathing circuit.

Regardless, the worse outcomes with vasopressin are indirect contrast to a study done in pigs where resuscitation from LAST was more successful with vasopressin and epinephrine compared to lipid emulsion. These conflicting findings may be

related to differences in experimental protocols. In the experiments with rats by Di Gregorio and Weinberg et al. [40], asystole occurred immediately with injection of 20 mg/kg of bupivacaine and CPR initiated without delay. In the study by Mayr et al. [41], a lower dose of 5 mg/kg was used and CPR was not initiated until approximately 3 min later during which time the pigs were apneic for all of that time and pulseless for 1 min. This study design was intended to more accurately reflect what would happen clinically in the context of seizure and a more realistic subsequent treatment time course.

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