Local Anesthetic Systemic Toxicity

David M. Dickerson, MD; and Jeffrey L. Apfelbaum, MD

Abstract
Local anesthetic systemic toxicity (LAST) is a rare yet devastating complication from the administration of local anesthesia. The ability to recognize and treat LAST is critical for clinicians who administer these drugs. The authors reviewed the literature on the mechanism, treatment, and prevention of LAST, with the goal of proposing a practical method for its management.

Keywords
local anesthetic toxicity, lipid emulsion, bupivacaine toxicity, acute pain, ambulatory surgery

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The history of local anesthetic systemic toxicity (LAST) is characterized by a pattern of discovery, application, observation, and innovation (Figure 1).1-5 Since the isolation of cocaine (from coca leaves) in 1859 and its first clinical application in 1884, local anesthesia (LA) has been used to diminish the pain of medical procedures.1 The clinical benefits, however, were soon weighed against the adverse effects: respiratory failure, seizures, palpitations, and irregular cardiac function.2 Despite the advent of safer synthetic local anesthetics, cases of toxicity persisted, culminating in a 1979 report of the catastrophic consequences of LAST that noted a relationship between drug lipophilicity and the potential for cardiac toxicity.6 The unintended intravascular injection or uptake of potent amino amide anesthetics (eg, bupivacaine) appeared as a common theme.

In early studies, the incidence of LAST ranged from 7.5 to 20 per 10,000 peripheral nerve blockades; more recently, the incidence was estimated to be low as 2.5 per 10,000 blockades.7,9 In one series, frequency was as high as 10 per 10,000 blockades, and in another, no events were recorded for over 12,000 blockades.10,11 The call for optimized management of LAST has resulted in heightened awareness, the development of safety steps in local anesthetic administration, the discovery of lipid emulsion therapy, and treatment and prevention guidelines with validated checklists. However, cases persist despite the application of ultrasonography, the availability of safer local anesthetics, and greater understanding of the risk factors.11,12 As demonstrated by the case of an elastomeric pump failure described in the July 2014 issue of Aesthetic Surgery Journal,13 LAST occurs despite practice advisories and heightened awareness. This case emphasizes the need for vigilance and preparedness to prevent an unforeseen occurrence of toxicity.13 The safety of perioperative local anesthesia can be optimized by knowledge of its mechanism, the clinical presentation of LAST, and techniques for preventing and treating this condition.

MECHANISM OF LOCAL ANESTHETICS
The analgesia produced by local anesthetics results from the binding of voltage-gated sodium (Na+) channels and blocking of the excitation threshold of nociceptive afferent neurons. Binding prevents pain transmission by the peripherally located primary afferent neuron.14-16 Additionally,
LA may inhibit the free-end nociceptor-sensitizing inflammatory cascade and reduce hyperexcitability in the dorsal horn of the spinal cord.\textsuperscript{17,18} Local anesthetics have been synthesized with various potencies and duration of action. The characteristics of common local anesthetics are summarized in Table 1.

### LOCAL ANESTHETICS IN ANALGESIA

As a cornerstone of multimodal analgesia, local anesthetics provide myriad benefits. Local anesthetics bolster multimodal analgesia by potentially improving quality of recovery, decreasing opioid exposure, decreasing postoperative nausea and vomiting, improving patient satisfaction, decreasing length of hospital stay, and reducing the risk of chronic postsurgical pain.\textsuperscript{17-20} With various routes and sites of administration and their utility as intermittent or continuous therapy, local anesthetics are associated with varying degrees and risks of toxicity. Toxicity is further influenced by additional factors such as anatomic site of administration, the dosage of the drug, its pharmacokinetic profile, and whether a vasoconstrictor is added (Table 2).

**DEPO-LOCAL ANESTHETICS IN ANALGESIA**

Liposomal bupivacaine has been approved by the US Food and Drug Administration for single-dose wound infiltration or administration as a depo-local anesthetic. Bupivacaine-impregnated collagen, a similar agent, is currently in a phase 3 study. Pharmacokinetically, the delayed yet sustained release of these agents results in continuous analgesic serum concentrations with attenuated peak concentrations, suggesting a potential decrease in toxicity. However, the coadministration of nonliposomal anesthetics may cause rapid release of bupivacaine molecules and potential for toxicity. Although these agents offer significant promise for sustained postoperative LA with decreased toxicity, additional economic data and further study are needed to...
Dickerson and Apfelbaum 1113

establish a cost-effective role for them in the routine management of postoperative pain.

MECHANISM OF LOCAL ANESTHETIC SYSTEMIC TOXICITY

Two leading hypotheses prevail for the mechanism of LAST: LA-impaired electrophysiologic function of the heart and loss of cardiac energy at the mitochondrial level. Local anesthetics reduce sodium ion flux by binding Nav, but this binding is not exclusively in the peripheral nervous tissue. Cardiac cells rely on Nav-initiated depolarization during cardiac action potential cycles.15,16,21 Inhibition of cardiac Nav channels may result in conduction disturbances, ventricular arrhythmias, and contractile dysfunction. This effect may be further exacerbated by inhibition of fatty acid transport by local anesthetic at the inner mitochondrial membrane, resulting in a loss of cardiac energy from decreased oxidative phosphorylation. There is much debate about whether systemic toxicity is the effect of electrophysiologic dysfunction or contractile dysfunction. It has been suggested that the specific mechanism may vary with different anesthetics and their diverse binding of cardiac Nav channels.16,21

The ratio of cardiovascular to central nervous system (CNS) toxicity also varies among local anesthetics. With lidocaine and mepivacaine, CNS symptoms typically appear before cardiovascular symptoms.22 CNS effects appear to be associated with disturbances in the transmission of γ-aminobutyric acid. Neuronal excitability is associated with inhibition of the TASK potassium channel by anesthetics, which contributes to the induction of seizures.23 However, injury or death appears to be associated with cardiac toxicity.

CHARACTERISTICS OF LOCAL ANESTHETIC SYSTEMIC TOXICITY

The classic presentation of LAST has possible variants. Classically, toxicity appears on a continuum of adverse effects in the CNS that, with more toxic levels, progresses to cardiovascular symptoms. In a review of systemic toxicity

Table 1. Characteristics of Local Anesthetics

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Class/Chemical Linkage</th>
<th>pKₗ (Onset Time)</th>
<th>Protein Binding (Duration of Action)</th>
<th>Lipophilicity (Potency)</th>
<th>Maximum Dose, mg/kg (Dose With Epinephrine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Amide</td>
<td>7.8 (fast)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>4.5 (7)</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Amide</td>
<td>8.1 (slow)</td>
<td>Long</td>
<td>Potent</td>
<td>2.5 (3)</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Amide</td>
<td>8.1 (slow)</td>
<td>Long</td>
<td>Potent</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Amide</td>
<td>8.0 (fast)</td>
<td>Moderate</td>
<td>Weak</td>
<td>5-7 (7-8.5)</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Amide</td>
<td>7.7 (fast)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>4.5 (7)</td>
</tr>
<tr>
<td>Articaine</td>
<td>Ester</td>
<td>7.8 (fast)</td>
<td>Short</td>
<td>Moderate</td>
<td>4 (7)</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>Ester</td>
<td>8.0 (very fast)</td>
<td>Short</td>
<td>Moderate</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Ester</td>
<td>8.7 (slow)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>12</td>
</tr>
<tr>
<td>Procaine</td>
<td>Ester</td>
<td>8.9 (slow)</td>
<td>Short</td>
<td>Weak</td>
<td>3</td>
</tr>
</tbody>
</table>

pKₗ denotes the negative logarithm of the ionization constant of an acid. *Commonly administered in plastic surgery.

Table 2. Local Anesthetic Routes of Administration and Magnitude of Absorption

<table>
<thead>
<tr>
<th>Route</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous/systemic</td>
<td>Continuous or intermittent</td>
</tr>
<tr>
<td>Intercostal</td>
<td>Continuous or intermittent</td>
</tr>
<tr>
<td>Perineural/regional/compartment (caudal &gt; epidural &gt; brachial plexus)</td>
<td>Continuous or intermittent</td>
</tr>
<tr>
<td>Subcutaneous/incisional (infiltrative/tumescent)</td>
<td>Continuous or intermittent</td>
</tr>
<tr>
<td>Transdermal/topical</td>
<td>Intermittent</td>
</tr>
</tbody>
</table>

Routes are listed by magnitude of absorption, from greatest (intravenous/systemic) to least (transdermal/topical).
cases published in the peer-reviewed literature during a 30-year period, Di Gregorio et al.\textsuperscript{22} found that 60% were classic (ie, rapid onset) with CNS symptoms and cardiovascular symptoms (Table 3). Conversely, some symptoms appeared more than 5 minutes after injection or were isolated cardiovascular symptoms. Classic prodromal symptoms (eg, circumoral numbness, metallic taste, auditory changes) appeared in only 18% of their toxicity cases in this series. General anesthesia or heavy sedation is thought to influence the clinical pattern of toxicity in that CNS changes may go unnoticed and pharmacokinetics may be altered.\textsuperscript{22,24}

Certain patient characteristics may increase the risk of symptoms from an overdose of local anesthetics (Table 4). Risks include extremes of age (children and the elderly), high cardiac output states due to increased vascular absorption, and the presence of other comorbidities such as cardiac disease, pregnancy, hepatic dysfunction, or metabolic syndromes.\textsuperscript{25}

### Prevention of Toxicity: Safety Steps

Several safety steps have been advocated to identify or reduce the risk of toxicity.\textsuperscript{26} The following have been suggested for safe administration of LA: limiting the cumulative dose, using ultrasound or direct visualization for catheter placement, test dosing, incremental injections, negative catheter aspiration, and adherence to guidelines. Incorporation of multiple safety steps may improve detection of intravascular injection or impending toxicity. Although it appears that anesthetic infusion pumps are safe in aesthetic and reconstructive surgery,\textsuperscript{27} a high rate of pump malfunction was observed in 1 series.\textsuperscript{28} Pump malfunction aside, applying safety steps such as those used for peripheral nerve blockade may reduce risk in surgeon-initiated continuous anesthetic infusion.

### Limiting the Cumulative Effect of Anesthetics

Anesthetics are often additive. Concurrent administrations of multiple local anesthetics contribute to a single systemic toxic threshold. Although specific serum concentration levels have been associated with toxicity, dosing guidelines that are weight based (mg/kg) fail to reliably predict these levels, resulting in potential toxicity at lower-than-anticipated doses.\textsuperscript{29,30} With topical LA and subcutaneously administered solution via the tumescent technique, experience-derived, weight-based doses that are substantially higher than recommended levels are often administered.\textsuperscript{31} Based on pharmacokinetic data, it appears that these application routes are associated with a lower risk of systemic toxicity, yet toxicity still may occur. The American Society of Regional Anesthesia and Pain Medicine (ASRA) advocates using the lowest concentration and dose necessary for neuraxial analgesia, and a similar philosophy should be applied to non-neuraxial applications.\textsuperscript{32} Postoperatively, analgesic concentrations (<0.25% bupivacaine or ropivacaine) are used for continuous infusion. Incisional injection is limited to recommended doses after consideration of the anesthetic being concurrently administered by the anesthesia team.\textsuperscript{29} Liposomal bupivacaine should not be coadministered with other local anesthetics due to the risk of toxicity.

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**Table 3. Classic Presentation of Local Anesthetic Systemic Toxicity**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>&lt;5 min</td>
</tr>
<tr>
<td>Prodromal symptoms (18%)</td>
<td>Dizziness, drowsiness, tinnitus, confusion, dysphoria, dysarthria, auditory disturbances, circumoral numbness, metallic taste in mouth</td>
</tr>
<tr>
<td>CNS symptoms (more likely to occur with lidocaine than bupivacaine)</td>
<td>Prodrome symptoms, seizures, loss of consciousness, agitation</td>
</tr>
<tr>
<td>CVS symptoms</td>
<td>Bradycardia/arrythmia, tachycardia, hypotension, wide complex, ST-segment changes, pain, dyspnea, hypertension, ventricular ectopy, ventricular tachycardia, ventricular fibrillation</td>
</tr>
</tbody>
</table>

Data from Di Gregorio et al.\textsuperscript{22} CNS, central nervous system; CVS, cardiovascular system.

**Table 4. Comorbid Risk Factors for Local Anesthetic Systemic Toxicity**

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremes of age (children and elderly)</td>
</tr>
<tr>
<td>Hepatic dysfunction or altered hepatic perfusion (decreased plasma proteins, decreased hepatic clearance)</td>
</tr>
<tr>
<td>Low cardiac output states (drug accumulation, reduced clearance)</td>
</tr>
<tr>
<td>High cardiac output states (increased gradient for vascular diffusion, increased absorption)</td>
</tr>
<tr>
<td>Cardiac pathology (heart disease, conduction blocks, cardiac failure)</td>
</tr>
<tr>
<td>Reduced plasma proteins (increased free [active] fraction of local anesthetic)</td>
</tr>
<tr>
<td>Pregnancy (decreased plasma proteins, increased cardiac output)</td>
</tr>
<tr>
<td>Concomitant use of β-blocker, digoxin, calcium antagonists, cytochrome P450 inhibitors</td>
</tr>
</tbody>
</table>

Data from Ciechanowicz and Patil.\textsuperscript{25}
Dickerson and Apfelbaum 1115

Incremental Injections and Catheter Aspiration

Although lacking objective data, administering small incremental doses (3-5 mL) of local anesthetic has been recommended (assuming a negative test-dose result) so that the anesthesiologist or surgeon can readily monitor for inadvertent intravascular injection. Data on the reliability of this technique are lacking because it can be impractical to wait a full circulation period (30-45 seconds) between every 3-mL injection. Although recommended, catheter aspiration for blood is unreliable for identifying catheters placed intravascularly, with the possible exception of multiorifice catheters. The presence of negative aspiration via an infusion catheter should be verified before pump initiation.

Intravascular Test Dosing

Few studies have identified evidence-based techniques for catheter test dosing, yet test dosing with an intravascular marker is recommended when administration of potentially toxic doses of LA is planned. Potential test-dose agents include epinephrine, local anesthetic, air, opioid, and isoproterenol. Although not without limitations, epinephrine-containing test solutions are commonly given during electrocardiography and while monitoring heart rate and blood pressure. Several test-dose agents and their associated effects and limitations are listed in Table 5. Since other safety steps may not completely prevent intravascular injection by the aesthetic surgeon, catheter test dosing with an epinephrine-containing solution before pump initiation may have value. During application of an epinephrine-containing solution for a tumescent technique, audible changes in heart rate may alert the surgeon to vascular uptake of both epinephrine and anesthetic.

Ultrasound-Guided Regional Anesthesia

Systemic toxicity has been reversed with ultrasound-guided regional anesthesia, but reversal is not possible if peripheral nerve blockade is performed without ultrasound. Although intravascular injection during peripheral nerve blockade is possible with ultrasound, the unexpected absence of local anesthetic spread during injection, as well as the visualization of adequate coverage of neural structures with less local anesthetic, serves to prevent intravascular injection and delay the possibility of toxicity from tissue uptake.

TREATMENT FOR SYSTEMIC TOXICITY FROM ANESTHETICS

The treatment of LAST has been the subject of many reviews, including a practice advisory from the ASRA. The treatment of systemic toxicity is very different from that of conventional cardiac arrest in that airway management with optimal oxygenation and ventilation is of utmost importance (Figure 2). Prevention of hypoxia and acidosis may eliminate or slow cardiovascular collapse and seizures. If seizures ensue, benzodiazepines are administered to prevent seizure-associated acidosis. Rarely, neuromuscular blockade may be required if benzodiazepines fail to stop the seizure.

Cardiac arrest is treated with chest compressions. Epinephrine is recommended in low doses (<1 µg/kg); persistent arrhythmia may occur with higher doses. Negative inotropes such as β-blockers or calcium channel blockers are not provided because they may cause myocardial depression. Amiodarone is administered for persistent ventricular arrhythmia, but local anesthesia is avoided in

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>Dose</th>
<th>Positive Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>15 µg</td>
<td>HR increase &gt;10 beats/min</td>
<td>Beta blockade may impact sensitivity</td>
</tr>
<tr>
<td>Local anesthetic</td>
<td>Chloroprocaine or lidocaine 100 mg</td>
<td>Auditory disturbance</td>
<td>Premedication with benzodiazepines may affect sensitivity</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine 25 mg</td>
<td>Circumoral numbness</td>
<td>Large doses neuraxially will result in total spinal anesthesia</td>
</tr>
<tr>
<td></td>
<td>Ropivacaine 60 mg</td>
<td>Metallic taste</td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>2 mL</td>
<td>Audible response on precordial Doppler monitoring</td>
<td>Availability of Doppler monitoring</td>
</tr>
<tr>
<td>Opioid</td>
<td>Fentanyl 100 µg</td>
<td>Drowsiness or sedation</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>3 µg</td>
<td>HR increase &gt;20 beats/min</td>
<td>Neurotoxicity unknown</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; HR, heart rate; SBP, systolic blood pressure.
Vasopressin administration is not recommended.

Rapid initiation of lipid emulsion therapy has been advocated, which may prevent a downward spiral of cardiac dysfunction, progressing acidosis, and worsening cardiac dysfunction.48

If LAST is suspected, the nearest available cardiac team should be notified and arrangements made for cardiopulmonary bypass in the event the patient’s condition fails to improve.

**Figure 2.** Quick guide to treating systemic toxicity due to local anesthesia.

Lipid Emulsion Therapy

When the effect of intravenous lipid emulsion on bupivacaine toxicity in carnitine-deficient rats was examined, a paradoxical outcome led to the development of a novel treatment. Lipid emulsion therapy reduced the median lethal dose (LD50) of bupivacaine and, more important, showed potential as a therapy for LAST.49 Several years after this discovery in rats and canines, intravenous lipid emulsion was applied to humans and added to resuscitation guidelines internationally.50-52

The mechanism of lipid emulsion therapy is not well defined, but several hypotheses exist. Lipid emulsion is thought to provide a “lipid sink” to dissociate local anesthetic molecules from the cardiac Na⁺.53,54 Binding of unbound free anesthetic results in its metabolism and clearance. The lipid emulsion may act as a direct energy source to the myocardium, providing fatty acid substrate, augmenting production of mitochondrial adenosine...
triprophosphate in the heart, and increasing cardiac output. Concomitantly, lipid emulsion elevates triglycerides, which interact with myocardial calcium channels to increase cardiac function. It has been suggested that overdoses of other lipophilic drugs also may be treated by lipid emulsion therapy.

Through clinical experience, the optimal administration of lipid emulsion has been formalized. Current recommendations call for a bolus injection of 1.5 mL/kg followed by an infusion at 0.25 mL/kg/min. The recurrence of cardiovascular collapse after cessation of liquid emulsion therapy has been described in the literature. The immediate availability of sufficient lipid emulsion appears requisite. Marwick et al observed the return of cardiovascular collapse in a patient who received the only available quantity (500-mL bag) of lipid emulsion.

The benefits of intralipid therapy appear to outweigh the potential risks. Risks include allergic reaction (such as egg, soy, or peanut cross-reactivity), hyperthermia, pancreatitis, hypercoagulability, antineutrophil action, and elevated liver aminotransferases.

**PREPARATION AND VIGILANCE**

The ability to identify patients at risk for systemic toxicity is critical to its prevention and treatment. A strong foundation is needed for safe and effective LA dosing and administration. When pain pumps are in use, catheter test dosing should be performed before infusion is begun. Patients discharged with continuous wound infusion or peripheral nerve catheters need established lines of communication and daily monitoring via telephone. Family members also should be educated on pump care (including catheter removal, stopping the pump, and dressing maintenance) as well as adverse effects (eg, prodromal symptoms). In our opinion, pumps should be connected and running under observation for at least 30 minutes before patient discharge to allow for assessment of infusion function. Similarly, practitioners trained in resuscitation and the treatment of LAST should be immediately available when pumps are initiated. Dedicating part of the recovery room to patients who have received large local anesthetic doses or infusions may allow prompt treatment if a patient becomes unresponsive.

Use of the ASRA 2012 checklist for treatment of LAST improved trainee performance during a simulation. Because toxicity from local anesthetics is rare, simulation, checklists, and readily available reference algorithms may lead to comprehensive rapid recall and implementation of therapy. Figure 2 provides a brief summary of the treatment recommendations of the Association of Anaesthetists of Great Britain and Ireland and the ASRA checklist, which may be included in a toxicity response kit. Prominent display of this guide in clinical common areas may promote continued heightened awareness; the guide also may serve as a helpful reference during treatment. Resuscitative equipment, standard monitors, lipid emulsion, and practitioners skilled in the diagnosis and treatment of systemic toxicity are essential for a successful outcome.

**CONCLUSIONS**

While patient comfort necessitates the administration of local anesthetics, a commitment to safe practice will optimize patient outcomes. An understanding of the mechanism, treatment, and prevention of LAST is requisite for plastic and reconstructive surgeons who administer this medication. Promoting awareness, vigilance, and preparedness may save a life if this rare but devastating complication occurs.

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