Local Anesthetic Systemic Toxicity: A Narrative Literature Review and Clinical Update on Prevention, Diagnosis, and Management

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PATIENT SAFETY

Background: The objective of this narrative review of local anesthetic systemic toxicity is to provide an update on its prevention, diagnosis, and management.

Methods: The authors used a MEDLINE search of human studies, animal studies, and case reports and summarize findings following the American Society of Regional Anesthesia and Pain Medicine practice advisories on local anesthetic systemic toxicity.

Results: Between March of 2014 and November of 2016, there were 47 cases of systemic toxicity described. Twenty-two patients (47 percent) were treated with intravenous lipid emulsion and two patients (4.3 percent) died. Seizures were the most common presentation. The spectrum of presenting neurologic and cardiovascular symptoms and signs are broad and can be obscured by perioperative processes. Local anesthetic type, dosage, and volume; site of injection; and patient comorbidities influence the rate of absorption from the site of injection and biodegradation of local anesthetics. Consider discussing appropriate dosages as a component of the surgical "time-out." A large-volume depot of dilute local anesthetic can take hours before reaching peak plasma levels. Oxygenation, ventilation, and advanced cardiac life support are the first priorities in treatment. Lipid emulsion therapy should be given at the first sign of serious systemic toxicity with an initial bolus dose of 100 ml for adults weighing greater than 70 kg and 1.5 ml/kg for adults weighing less than 70 kg or for children.

Conclusion: All physicians who administer local anesthetics should be educated regarding the nature of systemic toxicity and contemporary management algorithms that include lipid emulsion therapy. (*Plast. Reconstr. Surg.* 144: 783, 2019.)

Local anesthetics are ubiquitous in health care used by medical specialists in locations such as physician offices and ambulatory surgical centers.[1–15] Local anesthetic systemic toxicity can result in serious patient harm, including seizure, cardiac compromise and, in the worst-case scenario, fatality. Despite advances in pharmacology and advances in local anesthetic systemic toxicity prevention and treatment, recent published cases show that local anesthetic systemic toxicity continues to occur.[16–54] Accordingly, educating providers in all relevant specialties about the safe

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use of local anesthetics is paramount.[55] The objective of this narrative review of local anesthetic systemic toxicity is to highlight key principles of local anesthetic pharmacology and to provide an update on the prevention, diagnosis, and management of local anesthetic systemic toxicity.

PATIENTS AND METHODS

The authors used a MEDLINE search strategy for this narrative review of combinations of the following terms to obtain an inclusive overview of local anesthetic toxicity that will be useful to clinicians: local anesthetic, regional anesthesia, nerve block, toxicity, cardiac arrest, resuscitation, myocardial depression, epinephrine, vasopressin, vasopressor, cardiopulmonary bypass, lipid, lipid rescue, emulsion, bupivacaine, levobupivacaine, mepivacaine, lidocaine, ropivacaine, and etidocaine. Searches were performed using human and animal studies and case reports from the previous 50 years.

PHARMACOLOGY OF LOCAL ANESTHETICS

Chemical Structure

The canonical molecular structure of local anesthetics contains a lipophilic aromatic ring system attached by an ester or amide intermediate chain to a hydrophilic tertiary amine. The potency and toxicity of the pipecoloxylidide molecules (mepivacaine, bupivacaine, ropivacaine) relate to the length of the alkyl substitutions and the resulting lipid solubility. At physiologic pH, local anesthetics exist as a mixture of a protonated acid and neutral base because of their tertiary amine. However, only the uncharged form can cross the membrane, and once intracellular, the ionized, cationic form binds to a site on the inner pore of the sodium channel.[56] Lowering of the arterial pH may create intracellular ion trapping, thereby modifying cellular effects and potentially worsening toxicity.

Pharmacodynamics

Local anesthetics act on all parts of the nervous system and on all nerve types. The primary therapeutic effect of local anesthetics is to block the action potential being generated and propagated in peripheral nerves. Classically, this occurs by means of blockade of voltage-gated sodium channels in nerve membranes, which slows the rate of membrane depolarization (at low concentrations) and prevents cells from reaching the action potential threshold at high concentrations.[57] Sodium channels are also responsible for initiating the cardiac action potential. Cardiac toxicity includes effects on both electrophysiology and contractility. Local anesthetics have a direct effect on cardiac tissue (e.g., sinus node, Purkinje fibers, ventricular muscle), decreasing the rate of depolarization and increasing the action potential duration. Different local anesthetic molecules have different mechanisms; therefore, cardiac effects are drug specific.[58–60] Bupivacaine unbinds slowly from the sodium channel, resulting in a greater fraction of occupied channels. This is thought to be one mechanism explaining the increased potency (and toxicity) of bupivacaine compared with lidocaine.[61] Local anesthetics also can potentially inhibit (at concentrations unrelated to that required for sodium channel blockade) mitochondrial metabolism and oxidative phosphorylation.[62–70]

Pharmacokinetics

Routes of administration include topical, subcutaneous, intermuscular, neuraxial, and perineural.[71,72] Subsequent systemic absorption is delayed based on diffusion, the rate of which depends on the site of injection; the area over which absorption occurs; drug lipophilicity (e.g., bupivacaine is greater than lidocaine); plasma protein binding; molecular weight; and patient factors such as age, size, and comorbidities. Coadministration of epinephrine can delay absorption of local anesthetic into the circulation and reduce peak serum concentration.[73,74] Increasing the rate of administration or total dose increases the concentration gradient between tissue depot and blood, thereby increasing the rate of rise in plasma concentration and thus the risk of toxicity.[75] Ester local anesthetics are metabolized in the circulation by plasma esterases, whereas amide local anesthetics (i.e., lidocaine, mepivacaine, bupivacaine, ropivacaine) are processed in the liver by cytochrome P_{450}–linked enzymes,[76] dependent on liver blood flow. Metabolism of amide local anesthetics is reduced by any pathophysiologic state that decreases cardiac output or hepatic blood flow or impairs hepatic enzyme function.[77] Reduced cardiac output will delay both the rate of absorption of local anesthetic from the site of injection into the circulation and subsequent transit of amide local anesthetic to its site of metabolism. Patients with liver disease or congestive cardiac failure have elevated blood local anesthetic levels, placing them at increased risk of local anesthetic systemic toxicity. The metabolites of amide type local

anesthetics are excreted by means of the kidney into the urine. The hepatic metabolites are largely inactive, although some metabolites retain some local anesthetic activity.

Adverse clinical effects caused by local anesthetic accumulating in the heart and brain can be compensated for by redistribution to muscle.[78] However, other factors can influence distribution of local anesthetic; for example, elevated arterial carbon dioxide increases cerebral blood flow, increasing delivery of local anesthetic to the brain.[79] Hypercapnia and acidosis decrease plasma protein binding of local anesthetic, increasing its free fraction and thereby potentially worsening toxicity.

Key Messages on Pharmacology

- Local anesthetics impair nerve conduction by binding and inhibiting voltage-gated sodium channels.
- Local anesthetics impair a broad range of biological processes, blocking signaling at sites independent of sodium channels, many of which may moderate toxicity.
- Local anesthetic type, dosage, and volume; site of injection; binding to plasma proteins; and patient comorbidities influence the rate of absorption from the site of injection, subsequent tissue distribution, and biodegradation of local anesthetics.
- Lipophilic local anesthetics are more potent and longer acting, and have a greater potential for clinical toxicity.
- At toxic blood levels, bupivacaine is more likely to cause arrhythmias than lidocaine, whereas the latter may depress cardiac contractility without arrhythmias.

EPIDEMIOLOGY

The incidence of local anesthetic systemic toxicity can be estimated from registries,[54,80–82] population studies,[83] and administration databases,[84,85] but it is likely that many episodes of local anesthetic systemic toxicity are unreported. A recent American Society of Regional Anesthesia and Pain Medicine practice advisory[54] reports that, between March of 2014 and November of 2016, 47 separate cases of local anesthetic systemic toxicity were described. Local anesthetic systemic toxicity events occurred as a result of penile blocks (23 percent), local infiltration (17 percent), upper/lower extremity (17 percent), torso (8.5 percent), and neuraxial blockade (13 percent). Twenty-two patients (47 percent) were treated with intravenous lipid emulsion and two patients (4.3 percent) died.[54] Case reports remind us that even if local anesthetic systemic toxicity occurs infrequently, these events do occur and can result in catastrophic outcomes.[16–18,20–25,28,29,31,33,39–42,47,48,50,55,86]

DIAGNOSIS

If a potentially toxic dose of local anesthetic is planned, minimum recommended monitoring includes noninvasive blood pressure, electrocardiography, and pulse oximetry. Seizure (53 and 61 percent from case reports and registries, respectively) was the most common presenting feature reported in the above-mentioned American Society of Regional Anesthesia and Pain Medicine review.[54] Other common presenting central nervous system features of local anesthetic systemic toxicity are prodromal symptoms such as lightheadedness, dizziness, auditory and visual disturbance (blurred vision), tinnitus, and perioral numbness. The sympathetic stimulus associated with central nervous system toxicity may cause tachycardia and hypertension and influence the cardiac effect of the local anesthetic. Loss of consciousness, seizures, dysrhythmias, myocardial depression, ventricular tachycardia, ventricular fibrillation, pulseless electrical activity, and cardiac arrest may occur (Table 1).[86,87] All local anesthetics exert a dose-dependent depression of cardiac contractility and cardiac conduction.[86] Hypoxia, hypercarbia, and acidosis worsen the negative inotropy of local anesthetic systemic toxicity. Acidosis increases the charged form of local anesthetic, which is then trapped inside the cell.

Table 1. Symptoms and Signs of Local Anesthetic Systemic Toxicity

Prodrome
Perioral numbness
Tinnitus
Confusion
Dysarthria
Dysphoria
Dizziness
Drowsiness
Dysgeusia
Neurologic
Agitation
Loss of consciousness
Seizure
Cardiovascular
Arrhythmias (bradycardia, tachycardia, ventricular ectopy/tachycardia/fibrillation)
Hypotension or hypertension
Conduction disturbances (e.g., widened QRS complex)
Cardiac arrest (asystole, pulseless electrical activity)

Although local anesthetic systemic toxicity usually manifests as central nervous system and/or cardiovascular disturbances, it is important to recognize atypical manifestations.[86,87] The classic teaching that prodromal symptoms precede seizures, which then progress to cardiovascular collapse, is not always true. Cardiovascular toxicity can occur without prodromal symptoms or seizures.[86] Bupivacaine may cause severe arrhythmias coincident with or before the onset of central nervous system toxicity. Local anesthetic systemic toxicity can result from either inadvertent intravascular injection or delayed absorption into the circulation from the site of injection or application. Accordingly, the timing of onset is variable, ranging from immediate (more common with direct intravascular injection) to hours after administration (either from local tissue absorption, slowly increasing levels from continuous infusions, decreased clearance, or intravascular migration of indwelling catheters). There appears to be a trend toward delayed-onset local anesthetic systemic toxicity outside of the operating room,[88] and this may present with more subtle manifestations—instead of cardiovascular collapse, refractory relative hypotension may be the only sign.[86,87] Local anesthetic systemic toxicity has presented in patients after discharge from the postanesthesia care unit or the hospital. One patient experienced central nervous system toxicity 14 hours after lidocaine infiltration for liposuction surgery,[89] highlighting the importance of continued vigilance and patient monitoring. The safe period of observation following local anesthetic administration depends on the dosage and mode of delivery. For example, following performance of a major plexus block for anesthesia, we recommend a minimum period of observation of 30 minutes; however, following tumescent infiltration, anesthesia blood levels may not reach their maximum levels for several hours following injection, and therefore a substantially longer period of observation may be required. The ability to distinguish local anesthetic systemic toxicity from disease processes and patient comorbidities in the setting of confounding factors such as sedation and general anesthesia is important.[33,90]

Key Messages on Diagnosis

- The presenting features and timing of onset of local anesthetic systemic toxicity vary. The spectrum of neurologic and cardiovascular symptoms and signs are broad; atypical and some central nervous system features can be subtle.[86–88,91]
- The safe period of observation following local anesthetic administration depends on the dosage and mode of delivery.
- Diagnosis of local anesthetic systemic toxicity may be obscured by perioperative processes, sedation, and general anesthesia or be wrongly attributed to patient comorbidities.

RISK FACTORS

Patient-Dependent Risk Factors: Body Mass, Protein Binding, and Systemic Disease

Most patients, particularly young and healthy ones, tolerate weight-based doses of local anesthetics; however, patients at extremes of age and those with coexisting systemic disease may be at increased risk. Newborns, infants and the very old have a low lean muscle mass, which makes them prone to toxicity when total body weight is used for dosing. Infants have lower levels of plasma binding proteins and lower muscle mass than a healthy adult patient, so slight variation in calculations can result in excessive or even toxic doses.[86,92] Adults at-risk tend to have several coinciding problems (age; disease; cachexia; hypoalbuminemia; impaired cardiac, hepatic, and renal function) that increase the risk of local anesthetic systemic toxicity.[33,40,93–96] Case reports of local anesthetic systemic toxicity in patients with low albumin levels is concordant with the free fraction of local anesthetic being increased.[40,94,97,98] Patients' with metabolic and/or mitochondrial disease are at increased risk (independent of sodium channel) of local anesthetic systemic toxicity.[40,99–101] The pharmacokinetics section contains more detail on the metabolism of local anesthetics.

Patient-Independent Risk Factors: Local Anesthetic Type, Dosage and Volume, Absorption, and Site of Injection

Local anesthetics have differing effects on cardiac conduction, myocardial contractility, chronotropy, and peripheral vascular tone. Local anesthetic potency and toxicity are linked, and local anesthetics inhibit cardiac conduction proportional to their potency to induce nerve blockade. For example, bupivacaine and etidocaine contribute to an increased risk of cardiotoxicity relative to the risk of lidocaine and mepivacaine.[102] Bupivacaine and etidocaine tend to cause conduction disturbances, arrhythmias, and impaired contractility, whereas lidocaine is less likely to cause arrhythmias.[103] Ropivacaine is

a pure S(-) enantiomer and was developed as a safer alternative to racemic bupivacaine and introduced into clinical practice in the early 1990s. The R(+) isomer of bupivacaine binds cardiac sodium channels more avidly than the S(-) isomers (ropivacaine, levobupivacaine); however, the mechanism underlying cardiac toxicity may not necessarily be the result of local anesthetic binding to one specific site.[58] In experimental models, ropivacaine has been shown to be less cardiotoxic than bupivacaine.[59,104] However, the relative safety of ropivacaine compared with bupivacaine is complicated by the in vitro potency of ropivacaine being approximately 25 percent less than that of bupivacaine. Patients typically receive higher doses of ropivacaine than bupivacaine, with ropivacaine available in 0.75% and in some countries 1.0% concentrations (compared to bupivacaine available up to 0.5%). Because potency and toxicity are closely linked, it is possible that in equipotent doses and tissue concentrations, there may be slight differences only in the potential for ropivacaine and bupivacaine to cause toxicity.

Liposomal bupivacaine (Exparel; Pacira Biosciences, Inc., Parsippany, N.J.) has a delivery platform that results in slow dissociation of local anesthetic and delayed absorption from the site of injection into the circulation. Currently, there are no reports in the peer-reviewed literature of local anesthetic systemic toxicity following liposomal bupivacaine administration. However, the Adverse Event Reporting System database of the U.S. Food and Drug Administration has identified a pharmacovigilance signal indicating an association between local anesthetic systemic toxicity and liposomal bupivacaine.[105,106] We recommend that liposomal bupivacaine be afforded the same degree of vigilance regarding local anesthetic systemic toxicity.

A large mass (calculated by the product of concentration and volume) of local anesthetic increases the risk of toxicity,[80] but even a large volume of dilute local anesthetic may increase the area of drug absorption and lead to local anesthetic systemic toxicity. For example, there have been case reports of local anesthetic systemic toxicity after transversus abdominis plane block.[35,107,108] Local infiltration analgesia for orthopedic surgery[27] and local tissue infiltration[24,25,109] frequently involve the use of large volumes and dosages of local anesthetics. Albeit dilute, large volumes of local anesthetics are also used for cosmetic procedures, including tumescent liposuction. Klein and Jeske have been leaders in the study of safe tumescent anesthesia and have recently performed studies in 14 volunteers suggesting that, when followed by liposuction, infiltration of lidocaine doses up to 45 ml/kg is safe.[109] However, the reader should be aware that individual patient sensitivities, comorbidities, and physician or practice deficiencies may predispose to catastrophic outcomes. Furthermore, there are no universal mandated or regulatory reporting requirements that would reliably capture all catastrophic local anesthetic systemic toxicity events. Reporting of fatalities attributable to lidocaine toxicity in otherwise healthy patients following tumescent liposuction have occurred.[110] Cardiac arrest and death caused by local anesthetic systemic toxicity have occurred at outpatient plastic surgery centers, possibly related to the large volumes or improper administration.[28–30] However, these cases provide no context to the scope of the problem. A procedure identified relatively frequently in recent case reports associated with local anesthetic systemic toxicity is dorsal penile block for circumcision; the toxicity with this procedure is related at least in part to dosage and technique-related issues.[16,18,20–22] The mechanism of local anesthetic systemic toxicity in circumcision is likely inadvertent intravascular injection. Relative overdosage and lack of understanding of relevant pharmacokinetics may be relevant to local anesthetic systemic toxicity persisting as a clinical issue following topical anesthesia of the airway for awake tracheal intubation and/or bronchoscopy.[111,112] The less invasive nature of topical formulations (i.e., gels, liquids, sprays, ointments, and creams) of local anesthetics and the availability in nonhospital settings may give a false sense of safety that may result in overdosing.[17,23,113] Equal doses of the same local anesthetic when injected at different sites result in different blood levels, also impacting the risk of local anesthetic systemic toxicity.[80,114] Mixing local anesthetics can confound calculation of a safe total dosage and does not confer safety because local anesthetic toxicity is additive.

Key Messages on Risk Factors

- Dose, dose/weight, and volume of local anesthetic; extremes of age; low body mass; and cardiovascular, hepatic, renal, and metabolic dysfunction increase the risk of local anesthetic systemic toxicity.
- Cardiac toxicity is influenced by local anesthetic type; however, local anesthetic systemic toxicity events have been reported following all local anesthetic types.

PREVENTION

Established "safety steps" include use of incremental injections with intermittent aspiration and the use of a test dose with intravascular markers.[115,116] Incremental injection and intermittent aspiration can detect accidental intravascular needle-tip migration. Injecting the total local anesthetic dose over a longer period reduces its peak serum concentration and risk of local anesthetic systemic toxicity.[75] When combined, these two steps may help prevent or decrease the amount of local anesthetic injected in the event of an intravascular puncture, because it will be recognized during the next aspiration. A commonly used direct intravascular marker is low-dose epinephrine (2.5 to 5 μg/ml). In the case of an intravascular injection, epinephrine causes the heart rate to increase by more than 10 beats/minute and/or the systolic blood pressure to increase by more than 15 mm Hg.[115] Safe administration techniques and vigilant monitoring are the first-line measures of prevention. Suggested maximum safe doses of local anesthetics are summarized in Table 2.

Key Messages for Prevention

- Simple preventive steps include adopting an incremental injection technique with frequent aspiration.
- Consider use of a pharmacological marker such as epinephrine 2.5 to 5 μg/ml.
- Individualized local anesthetic dosing based on body mass, site of injection, and patients' unique factors are a safer alternative to total maximum doses; identify at-risk patients.

Table 2. Recommended Local Anesthetic Dosages

Local Anesthetic	Maximum Recommended Dose (mg/kg)	Maximum Recommended Dose in Adults (mg)	Indications	Comments
2-Chloroprocaine	12	800 (1000 with adrenaline*)	Infiltration, epidural, intrathecal, nerve block	
Lignocaine (lidocaine)	4.5 (7 with adrenaline)	200 (500 with adrenaline)	Infiltration, nerve block, ophthalmic, epidural, intrathecal, IVRA, topical use (i.e., gels, ointment, liquid, cream, spray, patch)	Safe dosage of tumescent lidocaine anesthesia has been estimated up to 45 ml/kg with liposuction from volunteer studies (14 subjects)†
Cocaine†	1.5		Fiberoptic endotracheal intubation, topical anesthesia for surgery on the ear, nose, and throat	Contraindications: IVRA, administration by injection, use with sympathomimetics and monoamine oxidase inhibitors
Prilocaine†	6 (8 with adrenaline)	400 (600 with adrenaline)	Infiltration, IVRA, topical (used in eutectic mixture with lignocaine)	Recommended for IVRA (outside North America) because less toxic than other amide LAs; avoid with concurrent use of drugs that cause methemoglobinemia
Mepivacaine	4.5 (7 with adrenaline)	400 (550 with adrenaline)	Infiltration, epidural, intrathecal, nerve block	
Ropivacaine†	3	225	Infiltration, nerve block, epidural, intrathecal, wound infusion	Contraindicated for IVRA; suitable for epidural or wound infusion; maximum daily dosage is 800 mg; pure S enantiomer
Bupivacaine†	2 (2 with adrenaline)	150	Infiltration, nerve block, ophthalmic, epidural, intrathecal	Contraindicated for IVRA; maximum daily dose in adults is 400 mg; suitable for epidural infusion
Levobupivacaine†	2	150	Infiltration, nerve block, ophthalmic, epidural, intrathecal	Contraindicated for IVRA; S-isomer of bupivacaine

IVRA, intravenous regional anesthesia; LAs, local anesthetics.

*Adrenaline (epinephrine) is commonly used in 5 μg/ml (1:200,000) or 2.5 μg/ml (1:400,000). IVRA is known eponymously as Bier block. Adrenaline is contraindicated for penile block, infiltration near terminal arteries, and IVRA. Dosages are guidelines only; in specific circumstances, specialists performing major regional anesthesia procedures may exceed these recommended doses. For intrathecal and epidural administration during pregnancy, LA dosage should be reduced because of increased sensitivity and anatomical/physiologic changes in the neuraxis.

†Source of recommended dosages: Australian Medicines Handbook Pty Ltd. Available at: https://amhonline.amh.net.au.acs.hcn.com.au/?acc=36265, and remainder from Butterworth JF IV, Mackey DC, Wasnick JD. Local anesthetics. In: Butterworth JF IV, Mackey DC, Wasnick JD, eds. *Morgan & Mikhail's Clinical Anesthesiology*. 5th ed. New York: McGraw-Hill Medical; 2013: 263–276; Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: A multifactorial concept. *Reg Anesth Pain Med.* 2004;29:564–575; and Klein JA, Jeske DR: Estimated maximal safe dosages of tumescent lidocaine. *Anesth Analg.* 2016;122:1350–1359.

- Consider discussing appropriate local anesthetic dosages as a component of the surgical time-out.

MANAGEMENT

The management of serious local anesthetic systemic toxicity is different from that of other cardiac arrest scenarios. Standard resuscitation guidelines for cardiopulmonary arrest emphasize immediate commencement of cardiopulmonary resuscitation, including effective chest compression and, if indicated, early defibrillation. For local anesthetic systemic toxicity, airway maintenance and oxygenation (Fig. 1) are the priority in treatment, because both hypoxia and acidosis exacerbate clinical local anesthetic systemic toxicity.[102] Drug administration in response to cardiac arrest caused by local anesthetic systemic toxicity is also different because the standard adult dose of epinephrine (1 mg) can impair resuscitation from local anesthetic systemic toxicity. Therefore, in a local anesthetic systemic toxicity cardiac arrest scenario, the individual doses of epinephrine should be reduced to less than 1 μg/kg. The pharmacologic management of local anesthetic systemic toxicity should avoid use of vasopressin, calcium channel blockers, beta adrenergic blockers, or other local anesthetics. A practitioner who suspects local anesthetic systemic toxicity should call for assistance and use cognitive aids such as checklists, crisis resource algorithms, and/or an electronic decision support tool to guide treatment. The American Society of Regional Anesthesia and Pain Medicine has developed a checklist and electronic decision support tool, the ASRA LAST smartphone app, available from https://www.asra.com/page/150/asra-apps, or the Apple App Store or Google Play.[88,91] Refer to the section below, Key Messages on Treatment, for further detail.

Supportive Treatment

Treatment of patients exhibiting isolated central nervous system symptoms of local anesthetic

Fig. 1. Summary of critical steps required in the management of local anesthetic systemic toxicity. *IV*, intravenous; *ACLS*, advanced cardiac life support.

systemic toxicity should focus on avoiding hypoxia and suppressing seizures. Immediate airway management is essential for preventing hypoxia and acidosis.[102,117] Benzodiazepines are the treatment of choice for seizure control. Patients with cardiac arrest should receive immediate advanced cardiac life support, with the above-mentioned differences being noted.[91,118] Successful initiation of cardiopulmonary bypass for cardiac arrest caused by local anesthetic systemic toxicity that is refractory to advanced cardiac life support has also been described.[119]

Lipid Emulsion Therapy

Until one decade ago, the treatment of local anesthetic systemic toxicity was limited to the modalities described above. However, it was shown by Weinberg et al. in 1998 that giving lipid emulsion in the form of a standard total parenteral nutrition solution could improve outcomes in a rat model of bupivacaine-induced cardiac arrest.[120] Since then, there have been numerous case reports of intravenous lipid emulsion use for the treatment of local anesthetic systemic toxicity in adult and pediatric patients.[19,21–25,27,33,35,42,93,100,121–155] Since 2010, the American Society of Regional Anesthesia and Pain Medicine and other society guidelines for the management of severe local anesthetic systemic toxicity recommend early use of intravenous lipid emulsion in the form of a bolus (1.5 ml/kg) followed by a continuous infusion (0.25 ml/kg/minute) up to 10 ml/kg in the first 30 minutes.[102,156] The American Society of Regional Anesthesia and Pain Medicine guidelines were revised in 2017 and recommend that, in adults weighing more than 70 kg, the initial 20% lipid emulsion bolus should be 100 ml over 2 to 3 minutes followed by 200 to 250 ml over 15 to 20 minutes.[91] The weight-based dosage should be used for the smaller adult (<70 kg) or child with local anesthetic systemic toxicity. The upper limit of total dosage is now recommended to be 12 ml/kg or up to 1 liter in the larger adult. Cognitive aids and intralipid should be available wherever potentially toxic doses of local anesthetics are used.

Significant progress toward our understanding of the mechanism of intravenous lipid emulsion therapy has been made recently.[157] The reversal of local anesthetic systemic toxicity is moderated by a multimodal effect of the lipid. First, the lipid provides a dynamic, intravascular compartment for partitioning of local anesthetics. This lipid compartment accelerates the redistribution of drug, moving it away from heart and brain and toward skeletal muscle for storage and liver for metabolic processing.[78,158] The redistribution effect is rapid, and elevated levels of drug are seen only transiently in blood. Following removal of drug from cardiac tissue, intravenous lipid emulsion provides a direct cardiac effect that improves cardiac output and further accelerates redistribution of the drug.[78,159] Finally, lipid emulsion adds postinsult cardiac protection, reducing ischemia-reperfusion injury to a recovering heart.[65,160] Intravenous lipid emulsion infusion may reduce acute lung injury if given before epinephrine.[161,162]

Uncommon risks of acute intravenous lipid emulsion infusion include allergic reactions, nausea, vomiting, thrombocytopenia, hypercoagulability, pancreatitis, fat deposition in extracorporeal membrane oxygenation circuits, and renal replacement therapy filter collapse.[163,164] Temporary interference with laboratory values is expected and can be mitigated by centrifuging samples.

Key Messages on Treatment

- Management of local anesthetic systemic toxicity should include the use of cognitive aids such as checklists or an electronic decision support tool.[91]
- Oxygenation, ventilation, and advanced cardiac life support are the priorities in treatment of local anesthetic systemic toxicity.
- Lipid emulsion therapy should be given at the first sign of serious local anesthetic systemic toxicity, with an initial bolus dose of 100 ml (for adults weighing >70 kg) and 1.5 ml/kg in adults weighing less than 70 kg and in children.
- Pharmacology: use epinephrine less than 1 μg/kg, and avoid vasopressin, calcium channel blockers, beta adrenergic blockers, or other local anesthetics.
- Avoid large doses of propofol; treat hypotension and bradycardia; commence cardiopulmonary resuscitation if pulseless.

EDUCATION

Medical professionals must be educated about local anesthetic systemic toxicity, its diagnosis, and its treatment.[55] Given that local anesthetic systemic toxicity is a rare occurrence, medical simulation is an effective educational tool for improving recognition and management of this problem.[165]

CONCLUSIONS

Local anesthetic systemic toxicity is a life-threatening complication of local anesthetic administration with potentially devastating results. The variable presenting features and onset of local anesthetic systemic toxicity coupled with general lack of experience, practice, and knowledge can leave providers ill-prepared to handle local anesthetic systemic toxicity, especially as the situation escalates to a crisis. Local anesthetic systemic toxicity occurs in a wide range of practice locations following local anesthetic administration by a wide range of practitioners. It is paramount that all physicians who administer local anesthetics are educated regarding the unpredictable and insidious nature of local anesthetic systemic toxicity and contemporary management algorithms that include intravenous lipid emulsion therapy. Education, mandatory safety requirements, and systems improvements can help minimize the occurrence and impact of local anesthetic systemic toxicity on patients and physicians.

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