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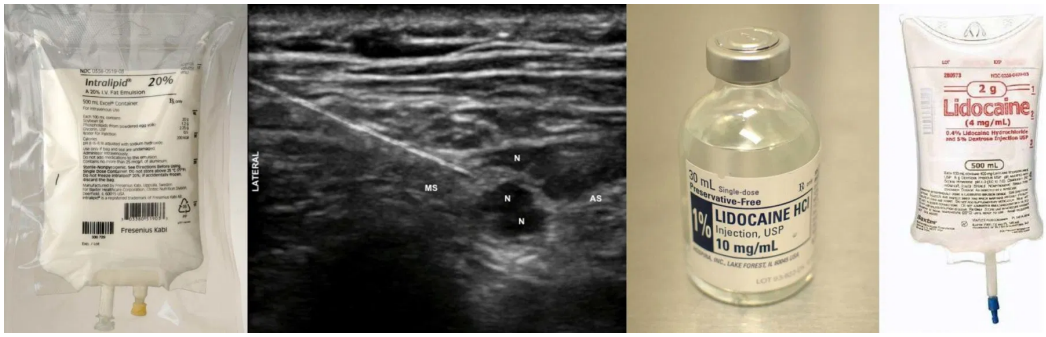
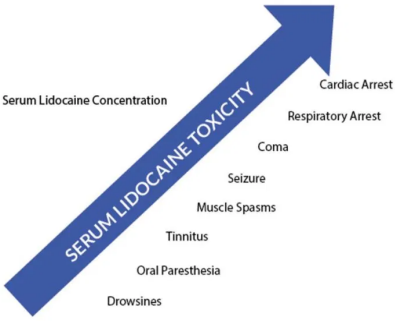
Local Anesthetic Systemic Toxicity (LAST)

December 11, 2016 by **Josh Farkas**





(https://emcrit.org/ibcc/last/attachment/lasttop/)

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epidemiology

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patient-dependent risk factors

- **Hepatic dysfunction**: Most anesthetics are hepatically cleared. Clearance rate is most relevant if the agent is *slowly* absorbed, administered in multiple doses, or provided as a continuous infusion.
- **Cardiac dysfunction**: Reduced *cardiac reserve function* may render LAST more dangerous (e.g., patients with severe chronic systolic heart failure or underlying conduction disease).
- **Renal dysfunction**: Uremia and acidosis may increase free drug levels, exacerbating toxicity.(33426662 (https://pubmed.ncbi.nlm.nih.gov/33426662/))
- **Low muscle mass** (e.g., older age, cachexia).
- **Pregnancy** (hyperdynamic circulation may accelerate systemic absorption following nerve blocks; reduced concentration of alpha-1 acid glycoprotein leads to higher free drug levels).
- Mitochondrial diseases, carnitine deficiency.

specific risk factors

- Nerve blocks:
  - High-volume blocks, with doses approaching the maximal safe dose range (see table below).
  - Placement of catheter for *prolonged* anesthetic infusion.
  - Failure to use ultrasound guidance. (29356773 (https://pubmed.ncbi.nlm.nih.gov/29356773/))
  - Bupivacaine has greater risks than ropivacaine or lidocaine. (29356773 (https://pubmed.ncbi.nlm.nih.gov/29356773/))
- Intravenous lidocaine infusions:
  - Prolonged, high-dose infusions.
- Less common causes of LAST:
  - Mucosal administration (e.g., bronchoscopy or awake intubation).
  - Large-volume, subcutaneous administration (e.g., to facilitate liposuction).

maximal safe dose of local anesthetic?

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.

Table 1 Suggested dosing recommendations for commonly used local anesthetic agents

Local anesthetic	Plain		With epinephrine	
	Maximum dose	Maximum dose	Maximum dose	Maximum dose
Bupivacaine	2 mg·kg^{-1}	175 mg	3 mg·kg^{-1}	225 mg
Levobupivacaine	2 mg·kg^{-1}	200 mg	3 mg·kg^{-1}	225 mg
Lidocaine	5 mg·kg^{-1}	350 mg	7 mg·kg^{-1}	500 mg
Mepivacaine	5 mg·kg^{-1}	350 mg	7 mg·kg^{-1}	500 mg
Ropivacaine	3 mg·kg^{-1}	200 mg	3 mg·kg^{-1}	250 mg
Prilocaine	6 mg·kg^{-1}	400 mg	8 mg·kg^{-1}	600 mg

Notes: Data from Berde and Strichartz.[92] Dadure C, Sola C, Dalens B, Capdevila X. Regional anesthesia in children. In: Miller RD (Ed.). *Miller's Anesthesia*, eighth ed. Philadelphia: Elsevier; 2015:2718.[93] American Academy of Pediatrics; American Academy of Pediatric Dentistry, Cote CJ, Wilson S; Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics* 2006;118:2587–2602.[94]

Two guidelines to the maximal safe dose of local anesthetics. Note the differences – these are rough guidelines, rather than precise science. The safe dose may also vary depending on patient specifics.
(top: Gitman M et al. PMID 31461049; bottom El-Boghdadly K et al. PMID 30122981)

(https://emcrit.org/ibcc/last/attachment/lastmax/)

incidence of LAST following nerve blocks

- LAST has an incidence of roughly one per thousand nerve blocks.(33426662 (https://pubmed.ncbi.nlm.nih.gov/33426662/)) This creates an interesting duality:
  - Overall, nerve blocks are a very safe procedure (often safer than the use of systemic analgesics).
  - At a large center which performs lots of nerve blocks, LAST is an event which *will* occasionally occur.

presentation

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timing

- LAST can occur within *minutes* of local anesthetic administration (due to inadvertent intravenous administration).
- LAST can occur in a *delayed* fashion:
  - i) Due to gradual systemic absorption, following a single administration of local anesthetic. This may occur several hours after administration.
  - ii) Due to *accumulation* following a continuous infusion of local or systemic medication (e.g., intravenous lidocaine infusion).
- Delayed-onset LAST may be harder to diagnose because it's not obviously temporally linked to anesthetic administration and clinically it may evolve in a more gradual fashion.(31461049 (https://pubmed.ncbi.nlm.nih.gov/31461049/))

LAST typically begins with CNS symptoms

- Early symptoms may include:
  - Sensory abnormalities: auditory changes, tinnitus, metallic taste, circumoral numbness, visual disturbance (e.g., blurred vision), or dizziness.
  - Delirium, dysarthria, tremor, or anxiety.
  - Ideally patients would be diagnosed *early,* based on mild symptoms. Unfortunately, sedation may mask these initial features.
- 💡 *Seizure* was the most common presentation in one literature review.(31461049 (https://pubmed.ncbi.nlm.nih.gov/31461049/))
- Increasing drug levels may eventually cause somnolence, coma, and respiratory suppression.

cardiovascular symptoms usually occur second

- 🔑 Neurologic symptoms usually occur first, but a fifth of patients may *initially* present with cardiovascular abnormalities.(30122981 (https://pubmed.ncbi.nlm.nih.gov/30122981/))
- *Initial features* may include sympathetic activation (e.g., tachycardia, hypertension, diaphoresis).
- *Later features may vary,* including:
  - Bradycardia and AV block, widened QRS complexes.
  - Reduced contractility, which may manifest predominantly as *hypotension*.
- Ultimately, any form of cardiac arrest can occur (ventricular tachycardia, ventricular fibrillation, PEA, or asystole).
- Lidocaine tends to reduce contractility more, whereas bupivacaine and ropivacaine tend to cause more arrhythmias.

differential diagnosis

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procedural complication (if nerve block is done to facilitate a procedure)

- Pneumothorax.
- Hemorrhage.
- Side effects from *other* medications which were co-administered to facilitate procedural sedation.

methemoglobinemia

- This may occur with benzocaine, lidocaine, or prilocaine.
- Typically, methemoglobinemia presents initially with desaturation and cyanosis.
- More on methemoglobinemia *here* (https://emcrit.org/ibcc/methemoglobinemia/) .

anaphylaxis

- Anaphylaxis due to local anesthetics is very rare.
- Anaphylaxis is more likely if other medications are co-administered (e.g., antibiotic).
- More on anaphylaxis *here (https://emcrit.org/ibcc/anaphylaxis/)* .

treatment

stop further administration

- If anesthetic is being infused, stop it.

lipid emulsion

- The antidote to LAST is 20% lipid emulsion (e.g., Nutrilipid, Intralipid, or Liposyn III 20%).
- Precise indications are unclear, but may include:
  - Substantial neurologic toxicity (e.g., seizures).
  - Substantial cardiovascular effects (e.g., arrhythmias, hypotension, or cardiac arrest).
  - Rapid clinical deterioration.
- *Optimal dosing isn't well defined*. Dosing below is based on consensus guidelines, but may require titration to effect.
- **Initial bolus:**
  - >70 kg ideal body weight: Give 100 ml.
  - < 70 kg: Give 1.5 ml/kg ideal body weight.
  - May repeat bolus if needed.
- **Infusion:**
  - >70 kg: ~600-1,000 ml/hour.
  - <70 kg: 15 ml/kg/hour (0.25 ml/kg/minute) using ideal body weight.
  - For ongoing cardiovascular instability, re-bolus and double the infusion rate.
  - Continue the infusion for at least ten minutes after hemodynamic stability is achieved (usually for a total duration of 30-60 minutes).
- **Dosing upper limit**: Avoid a cumulative dose above:
  - > 84 kg: ~1 liter.
  - < 84 kg: 12 ml/kg ideal body weight.
  - Wean down the infusion rate over time to avoid going over this cumulative dose, if possible.
- Potential side effects of lipid emulsion include allergic reactions, nausea, vomiting, pancreatitis, thrombocytopenia, and clogging of ECMO or dialysis circuits.(31461049 (https://pubmed.ncbi.nlm.nih.gov/31461049/)) Lipid interferes with measurement of laboratory tests, although this might be minimized by centrifuging the blood followed by removal of the lipid component.

airway management

- Hypoxemia and hypercapnia may both exacerbate LAST.
  - ⚠ Hypoventilation may lead to a vicious spiral that exacerbates LAST.
- There should be a relatively *low* threshold for intubation to secure the airway.

hemodynamic management

- If **arrhythmias** occur:
  - Don't give lidocaine or procainamide!
  - Avoid pure beta-blockers or calcium channel blockers, which may exacerbate hypotension.
  - ***Amiodarone*** is the front-line antiarrhythmic for ventricular arrhythmias.(29356773 (https://pubmed.ncbi.nlm.nih.gov/29356773/))
- If **epinephrine** is required (e.g., for PEA arrest), it should be dose-reduced by a factor of about ten to avoid arrhythmia:
  - Instead of 1 mg doses, 1 microgram/kilogram doses are recommended.(29356773 (https://pubmed.ncbi.nlm.nih.gov/29356773/))
- Vasopressin is generally avoided (the primary problem is cardiogenic failure, so increasing the afterload may merely exacerbate that). (33426662 (https://pubmed.ncbi.nlm.nih.gov/33426662/))

seizures

- First-line therapy is with benzodiazepines; for example, beginning with an initial dose of:
  - Lorazepam 0.1 mg/kg IV.
  - Midazolam 10 mg IV or IM.
- Use propofol cautiously, as this may promote cardiac collapse.
- ⚠ Avoid phenytoin, because phenytoin exerts anti-sodium channel activity.
- Ketamine and/or levetiracetam could be reasonable antiepileptic agents in this context, but no high-level evidence exists.

- Convulsions may worsen acidosis and thereby exacerbate the overall LAST toxicity. If seizures are resistant to benzodiazepine and intubation (with ketamine and/or propofol), neuromuscular paralysis might be an acceptable therapy to avoid muscular exertion that causes acidosis.(29356773 (https://pubmed.ncbi.nlm.nih.gov/29356773/)) However, paralysis will *not* protect the brain from ongoing seizure activity, so simultaneous and aggressive efforts must be made to stop the seizures (e.g., including placement of video EEG monitoring and administration of additional antiepileptic medications).
- More on the management of status epilepticus ***here*** (https://emcrit.org/ibcc/status-epilepticus/) .

cardiopulmonary bypass or ECMO

- Toxicity can last 1-2 hours.
- Prolonged CPR may be indicated.
- If cardiopulmonary bypass or ECMO are available, these are indicated for refractory LAST.

podcast

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questions & discussion

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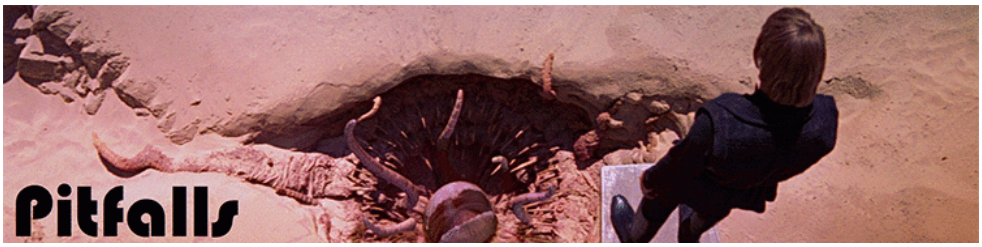
To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/hyperthermia/) .



(https://i0.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- Nerve blocks are increasingly being performed by clinicians throughout the hospital (and even at outpatient clinics). Staff in *any* location where nerve blocks are being performed should be prepared to manage LAST.
- LAST may occur in a delayed fashion following large-volume blocks or indwelling catheters that infuse local anesthetic. Such cases may evolve gradually and be less obvious than reactions which occur immediately after anesthetic administration.

References:

- **25028740** Dickerson DM, Apfelbaum JL. Local anesthetic systemic toxicity. Aesthet Surg J. 2014 Sep;34(7):1111-9. doi: 10.1177/1090820X14543102 [PubMed (https://pubmed.ncbi.nlm.nih.gov/25028740/)]
- **29356773** Neal JM, Barrington MJ, Fettiplace MR, Gitman M, Memtsoudis SG, Mörwald EE, Rubin DS, Weinberg G. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. Reg Anesth Pain Med. 2018 Feb;43(2):113-123. doi: 10.1097/AAP.0000000000000720 [PubMed (https://pubmed.ncbi.nlm.nih.gov/29356773/)]
- **30122981** El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018 Aug 8;11:35-44. doi: 10.2147/LRA.S154512 [PubMed (https://pubmed.ncbi.nlm.nih.gov/30122981/)]
- **31461049** Gitman M, Fettiplace MR, Weinberg GL, Neal JM, Barrington MJ. Local Anesthetic Systemic Toxicity: A Narrative Literature Review and Clinical Update on Prevention, Diagnosis, and Management. Plast Reconstr Surg. 2019 Sep;144(3):783-795. doi: 10.1097/PRS.0000000000005989 [PubMed (https://pubmed.ncbi.nlm.nih.gov/31461049/)]

- 33426662 Macfarlane AJR, Gitman M, Bornstein KJ, El-Boghdadly K, Weinberg G. Updates in our understanding of local anaesthetic systemic toxicity: a narrative review. Anaesthesia. 2021 Jan;76 Suppl 1:27-39. doi: 10.1111/anae.15282 [PubMed (https://pubmed.ncbi.nlm.nih.gov/33426662/)]

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.
