Chapter 8: Local Anesthetics

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INTRODUCTION

FOCUS POINTS

1. In infants, amide local anesthetics are not metabolized at a regular rate. This is especially important to remember when running infusions either intravenously or via regional or neuraxial anesthesia.
2. Ester local anesthetics are metabolized by pseudocholinesterases in the plasma. Amide local anesthetics are metabolized in P450 dependent pathways.
3. Maximum dose of local anesthetic varies based on the local anesthetics and sometimes the addition of epinephrine.
4. Treatment of local anesthetic systemic toxicity has two arms—one is supportive care and another is treatment with intralipid 20% at 1.5 mL/Kg.
5. Systemic absorption depends on location of injection, with intercostal injection leading to the highest blood levels.

HISTORY OF LOCAL ANESTHETICS

Cocaine is the first local anesthetic to be discovered. It remains the only naturally occurring local anesthetic. In regions where the coca leaf grows, such as Peru, the leaf has a long history of being dried and chewed. Reports of cocaine “making the tongue numb” existed. Carl Koller, an ophthalmologist, had sampled this and believed that cocaine could potentially be applied to the eye for surgery. He studied this on animals in the laboratory, then upon his own eye and eventually on patients. In 1884, he used cocaine to provide local anesthesia for glaucoma surgery, the first report of use of a local anesthetic for surgical anesthesia.[1] Until 1905, cocaine was the only available local anesthetic. In 1905, Alfred Einhorn synthesized procaine, another ester local anesthetic.

William Halstead is another pioneer in the area of local anesthetics. He is credited with performing the first regional block, a dental nerve block. He performed many blocks and held weekly teaching sessions of regional anesthesia with the use of cocaine. This led to him becoming a habitual user of cocaine and much of his work was not reported.

Following this, the use of local anesthetic developed in the hands of pioneers such as Leonard Corning, Heinrich Quincke, and Karl Bier.

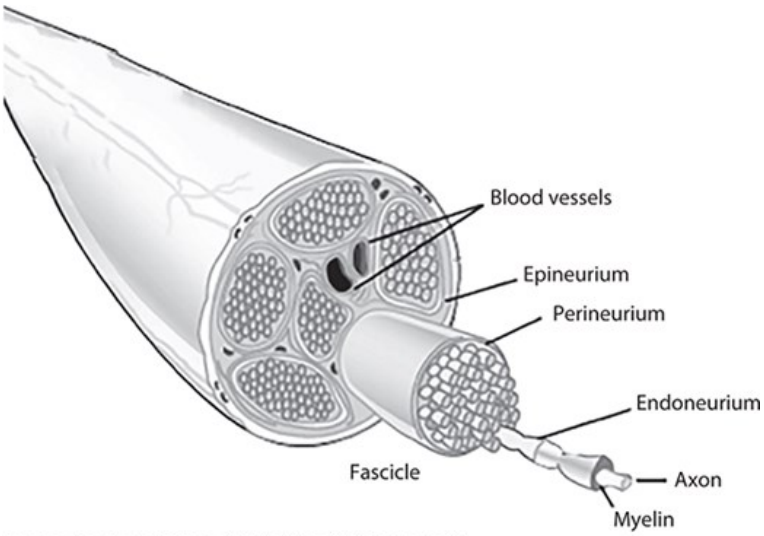
MECHANISM OF ACTION

Nerve Anatomy

to understand how local anesthetics exert their action it is important to understand nerve cell conduction and to have a basic understanding of the nerve itself. Nerve fibers consist of axons that are encased in endoneurium. Nerve fibers are then collected into fascicles, which are surrounded by specialized connective tissues known as perineurium. Finally, the fascicles are grouped and bound by another layer of connective tissue known as the epineurium (Figure 8-1).[2] An important difference between the epineurium and the perineurium is that the perineurium is capable of protecting neurons from chemical injury.[3]

Figure 8-1

Nerve anatomy. (Adapted with permission, from Siemionow M, Brzezicki G. Chapter 8 current techniques and concepts in peripheral nerve repair. *Int Rev Neurobiol.* 2009;87:141-72. https://www.sciencedirect.com/journal/international-review-of-neurobiology.)



Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Nerves are then classified based on presence or absence of the myelin sheath. Nerves are also classified based on their function, conduction velocity, or size (Table 8-1).

Table 8-1

Neve Characteristics Including Local Anesthetic Sensitivity

Class	Aα	Aβ	Aγ	Aδ	B	C
Function	Motor	Touch/pressure	Proprioception/motor tone	Pain/temperature	Preganglionic autonomic	Pain/temperature
Myelin	+++	+++	++	++	+	–
Diameter (μm)	12–20	5–12	1–4	1–4	1–3	0.5–1
Conduction speed (m/sec)	70–120	30–70	10–30	12–30	10–15	0.5–1.2
Local anesthetic sensitivity	‡‡	‡‡	‡‡‡	‡‡‡	‡‡	‡

+++, Heavy myelinated; ++, moderately myelinated; +, lightly myelinated; ‡‡‡, most susceptible to impulse blockade; ‡‡, moderately susceptible; and ‡, least susceptible.

Source: Adapted from Strichartz G, Pastijn E, and Sugimoto K. Neural physiology and local anesthetic action. In: Cousins MJ, Carr DB, Adapted with permission, from Cousins MJ, Carr DB, Horlocker TT, et al. eds. *Cousins & Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine*, 4th ed. 2008. Copyright © Lippincott Williams & Wilkins. All rights reserved.

The myelin sheath is not continuous, rather it is interrupted at regular intervals by regions knows as the nodes of Ranvier.[4] These areas are required for transmission of electrical impulses. Myelinated nerves are capable of faster conduction of nerve impulses secondary to salutatory conduction where

impulses skip from one node of Ranvier to the next. Unmyelinated nerves are, in general, smaller in diameter and transmit electrical impulses slower than their myelinated counterparts.

The various types of nerves are not equally blocked by local anesthetics. In general, local anesthetics first work on temperature sensation then proprioception, motor function, sharp pain, and light touch. This was thought to be due to the nerve's diameter, but the correlation between nerve diameter and onset of blockade does not entirely hold true. Large A delta fibers are blocked before small C fibers which are unmyelinated.[2]

Voltage-Gated Sodium Channel

Neurons maintain a resting membrane potential via use of a Na^+-K^+-ATPase pump that exchanges three sodium ions for every two potassium ions that are imported. This leads to a resting membrane potential of –70 mV. In order for an action potential to be generated, depolarization must occur. This is accomplished by activation of voltage-gated sodium channels following an influx of sodium ions leading to creation of an action potential. Specifically, they reversibly bind the intracellular portion of the sodium channel. Following depolarization and the action potential, there is a drop in sodium permeability and an increase in potassium influx via voltage-gated potassium channels, which works to return the membrane to its resting potential.

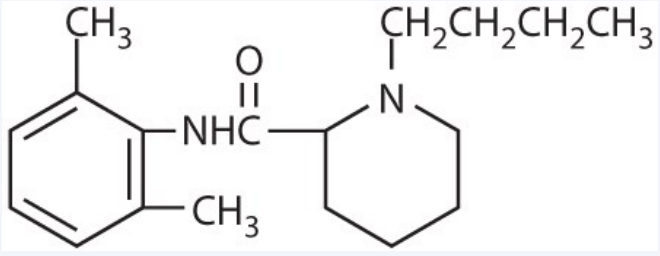
Local anesthetics provide anesthesia by blocking nerve impulses and thus altering sensation. Nerve impulses are blocked via blocking voltage-gated sodium channels, which alternate between several conformational states, including activated and inactivated states, leading to interruption of impulses in nerve axons. Specifically, local anesthetics bind the alpha subunit of the sodium channels intracellularly and thus block the influx of sodium that is necessary to cause depolarization and subsequent impulse conduction.[5]

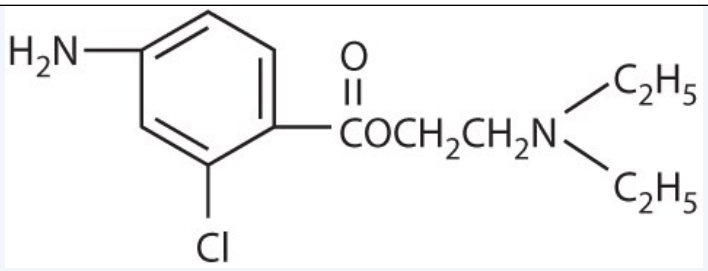
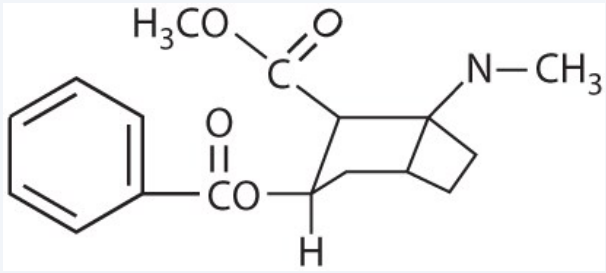
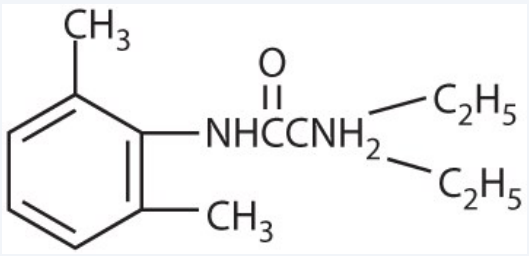
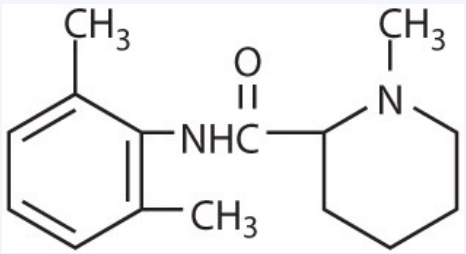
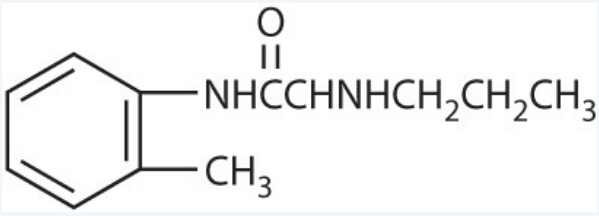
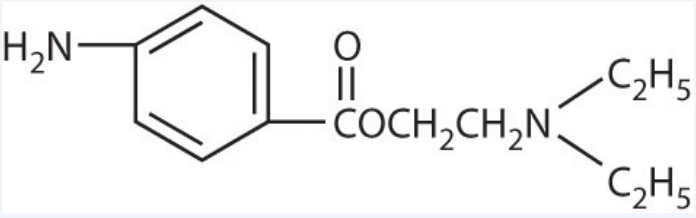
Classes of Local Anesthetics

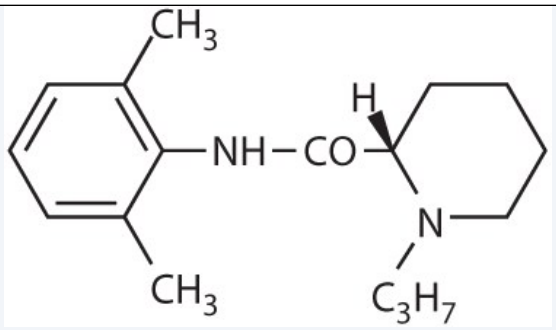
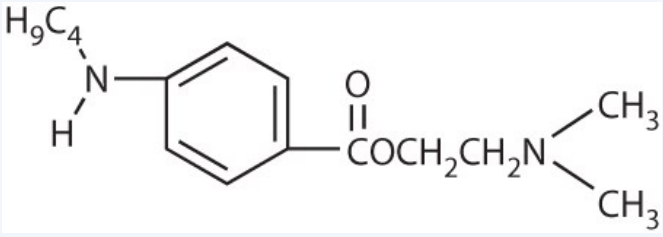
There are two major classes of local anesthetics, the amino esters and the amino amides (Table 8-2). Local anesthetics consist of a lipophilic aromatic ring attached to a tertiary hydrophilic amine. The bond that connects these defines whether the local anesthetic is an amide or an ester. Those anesthetics that are connected by an ester (–C–O) are esters and those connected by an amide link (–NHC–) are amides.

Table 8-2

Common Local Anesthetics

Drug and Chemical Structure	Classification	pK_a	Onset (min)	Duration (min)	Maximum Dose for Plain Solution (mg/kg)	Maximum Dose with Epinephrine (mg/kg)
Bupivacaine 	Amide	8.1	5–11	240–360	2	2.5
Chloroprocaine	Ester	8.7	6–12	30–60	10	15

						
Cocaine 	Ester	8.6	5–10	30–60	3	NA
Lidocaine 	Amide	7.8	2–4	60–120	5	7
Mepivacaine 	Amide	7.6	2–4	90–180	5	7
Prilocaine 	Amide	7.8	2–4	30–60	7	8
Procaine 	Ester	8.9	7–8	30–60	8	10

Ropivacaine 	Amide	8.1	10–15	180–300	3	3
Tetracaine 	Ester	8.5	5–9	90–360	1.5	2

The classes differ in their metabolism, excretion, as well as the risk of allergy. The ester class local anesthetics are metabolized by pseudocholinesterase. The metabolites are then excreted in the urine. Two esters, procaine and benzocaine, are metabolized to *p*-aminobenzoic acid or PABA. This metabolite has been associated with allergic reactions. In addition to this, those individuals with pseudocholinesterase deficiencies will metabolize the ester local anesthetics more slowly, which will increase the chance of untoward effects. Cocaine, an ester, differs as it is partially metabolized in the liver by *N*-methylation and excreted unchanged in the urine.

Amide local anesthetics are metabolized via *N*-dealkylation and hydroxylation by P450 enzymes in the liver. The rate varies with local anesthetic and occurs more slowly than ester hydrolysis.

Para-aminobenzoic acid is not a metabolite of amides and reports of allergic reactions to amide type local anesthetics are quite rare.

Clinical Pharmacology

When choosing a local anesthetic for use in clinical practice, it is important to be aware of the properties of the drug that are relevant. Key factors that should be considered include speed of onset, potency, duration of action, and motor vs. sensory blockad. In addition to factors inherent to the local anesthetics themselves, it is also important to be mindful of additional factors that affect their activity in vivo. Such factors include dosage of local anesthetics, addition of substances such as vasoconstrictors or other agents, and using mixtures of local anesthetics.

Onset and Duration of Action

The anesthetic agent itself is a huge determinate of the onset and duration of blockade. With regards to onset, agents that are moderately hydrophobic, such as lidocaine, have a faster onset of action than highly hydrophobic or hydrophilic agents.

Onset of action also depends on each anesthetic agent's pK_a, also known as the dissociation constant. The pK_a is the pH at which the ratio of the ionized water-soluble form is equal to the nonionized lipid soluble form. Local anesthetics that have a pK_a close to the pH where they are injected will have a faster onset because more local anesthetic is unionized, allowing the local anesthetic to cross and become intracellular. It is important to note that pK_a is not the only determining factor for clinical onset, thus agents with similar pK_a may have varying onset times and local anesthetics may act faster or slower than expected based on their pK_a. For example, chloroprocaine has a pK_a of 9.0 yet has a very rapid onset.

Duration of action is in part determined by the hydrophilic or hydrophobic nature of the local anesthetic. Agents that are more hydrophobic, such as bupivacaine, are more potent and in general produce longer lasting blocks.

Potency

The main determinant of anesthetic agent potency is hydrophobicity. Agents that are more hydrophobic, such as bupivacaine, are more highly potent and thus require a lower concentration to achieve a block. This correlation does not hold 100% true in clinical practice as other factors such as intrinsic vasoconstrictor/vasodilator properties and local anesthetic charge also affect potency.[6]

Sensory and Motor Blockade

Use of local anesthetics may lead to both sensory and motor blockade, but the amount of blockade of each varies with the specific agent used as well as the concentration of the agent utilized.

Bupivacaine has long been favored for use in epidurals as it provides reliable sensory blockade at low concentrations with minimal motor blockade. This is especially true when used in low concentrations such as 0.125%. In contrast, when given epidurally, etidocaine produces equal motor and sensory blockade.[6] More recently, use of ropivacaine has come in to favor given its ability to produce even less of a motor blockade compared to bupivacaine while maintaining adequate sensory blockade.

PHARMACOKINETICS

Systemic Absorption

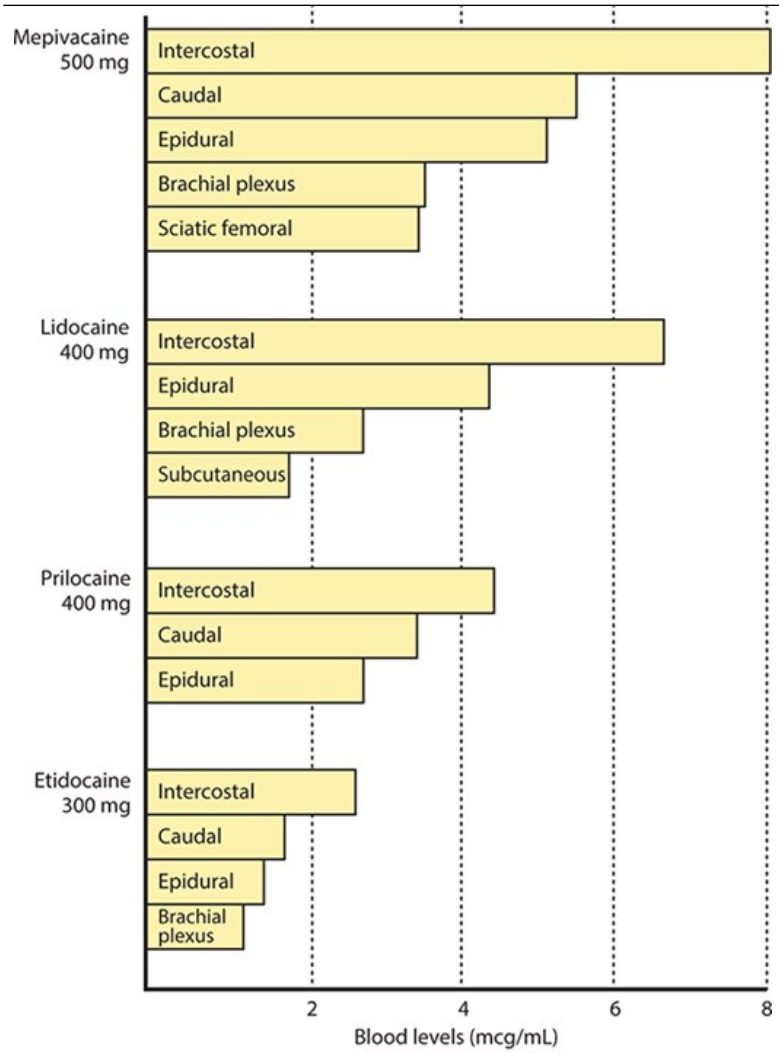
Rate of absorption depends on the local anesthetic, the location of the injection, as well as the presence of additives such as vasoconstrictors (Figure 8-2). Local anesthetics that are highly protein bound dissociate from the nerve at a slower rate, which results in slower absorption and increased duration of action.[5]

Epinephrine may be added to local anesthetics. The addition of epinephrine leads to local vasoconstriction and subsequently decreased absorption of the local anesthetic. This increases neuronal uptake and prolongs the duration of action via activation of α_2-adrenergic receptors. This effect is more pronounced with shorter-acting local anesthetics such as lidocaine, especially when used in areas that are highly vascular.[5]

Onset also reflects the vascularity of the tissue into which it is injected. Tissues that are highly vascularized such as the trachea or intercostal area have a higher rate of systemic absorption.

Figure 8-2

Local anesthetic blood levels based on injection site. (Adapted with permission, from Covino BD, Vassals HG. *Local Anesthetics: Mechanism of Action in Clinical Use*. 1976. Grune & Stratton. Copyright © Elsevier. All rights reserved.)



Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Biotransformation and Excretion

Metabolism varies based on local anesthetic class as discussed in section "Special Pharmacokinetic Considerations." Aminoamide drugs are primarily transformed in the liver and excretion occurs via the kidney. Given metabolism by the liver, it is important to remember that severe liver disease can alter the transformation of amide local anesthetics. As discussed below age is a factor in the elimination process.

Ester class local anesthetics are hydrolyzed by pseudocholinesterase in the plasma.

Special Pharmacokinetic Considerations: Dosing in Neonates and Infants

At birth the P450 hepatic enzyme system is not mature. As a result, amide type local anesthetics are metabolized at a slower rate.[7] This is seen with single doses of these anesthetics, but is particularly notable when neonates and infants are receiving continuous infusions of local anesthetics.[8] As they have decreased metabolism, they are at increased risk for elevated plasma levels and thus at an increased risk of experiencing local anesthetic toxicity if this is not taken into account. Bupivacaine has a half-life of 3.5 hours in adults, but in infants and neonates the half-life may be as long as 12 hours.[6]

In addition to immature hepatic P450 systems, neonates also have low levels of α_1-acid glycoprotein. This leads to decreased local anesthetic plasma binding capacity, which subsequently leads to increased levels of the free drug.

Bupivacaine

Bupivacaine use in infants has been studied. In the early 1990s local anesthetic toxicity in infants with the use of continuous epidural bupivacaine infusions was reported. Following these reports and an investigation by the Anesthesia Patient Safety Foundation, new recommendations came about to limit infusion rates of bupivacaine in infants to ≤ 0.2 mg/kg/h.[9] Following this recommendation, further study has shown that even at this recommended dosing plasma levels of bupivacaine can continue to rise beyond 48 hours of continuous infusion. Given this, thought should be given to its clinical use in neonates.

Bupivacaine exists in a racemic form with *l* and *d* enantiomers, with the dextrorotary form having a higher risk of cardiotoxicity.[5] Currently, levobupivacaine is not commercially available in the United States despite its wide use in Europe and better safety profile.

Recently, a liposomal form of bupivacaine has also been released with approval for use in adults for incisional pain with studies showing pain relief for up to 72 hours. Although not approved for use in children, one should be aware of this preparation, as it could be beneficial to the practice of anesthetic in pediatrics in the future.

Liposomal bupivacaine (Exparel®) was originally approved by the US Food and Drug Administration (FDA) in October 2011 for use as a local anesthetic by wound infiltration for hemorrhoidectomies and bunionectomies. Liposomal bupivacaine is based on DepoFoam technology, which encapsulates drugs in a liposomal platform and releases them over an extended period of time. By doing so, the toxic dose of bupivacaine decreases and potentially provides a greater safety profile. For example, a study by Boogaerts et al10 compared plain bupivacaine to liposomal bupivacaine in rabbits and illustrated that more than twice the dose of liposomal bupivacaine was needed compared to plain bupivacaine to produce seizures and ventricular arrhythmias.

Since its original approval, the use of liposomal bupivacaine has expanded greatly to include transversus abdominis plane (TAP) blocks, infiltration in mammoplasties, total knee arthroplasties, and many other procedures. The use in neuraxial blocks and peripheral nerve blocks is also under investigation. The results of the studies are promising and show clinically meaningful lower cumulative pain scores, reduced opioid requirements, faster hospital discharges, and reduced hospital costs.[11]

Ropivacaine

Ropivacaine is an *l*-enantiomer that has less cardiac and neurologic toxicities compared to bupivacaine.[5] Ropivacaine, as with bupivacaine, has clearance that is age-dependent and decreased in neonates. However, unlike bupivacaine, ropivacaine was not found to have increased accumulation in neonates on prolonged infusions.[7] Although it has not been found to have the same accumulation as bupivacaine, one should still be mindful of the possibility of local anesthetic toxicity especially in neonates and infants given that clearance is age-dependent and the potential for higher than expected plasma concentrations exists.

In comparison to bupivacaine, ropivacaine also exhibits less motor blockade.

Topical Anesthetics

The primary topical anesthetic used currently is EMLA (eutectic mixture of local anesthetics). EMLA is a mixture of 2.5% lidocaine and 2.5% prilocaine that is unique in its ability to penetrate intact skin. This is particularly useful in the pediatric practice. It is used for procedures such as intravenous access, lumbar puncture, circumcision, or removal of small lesions. To achieve effective cutaneous anesthesia it must be placed under an occlusive bandage for 45 to 60 minutes prior to the painful stimuli. EMLA has been used in infants and children and has been shown to be safe. Other topical formulations such as tetracaine gel and liposomal lidocaine are also available.[12,13]

Other forms of topical anesthesia such as TAC (tetracaine, epinephrine, and cocaine) are also available, but are ineffective through intact skin. This is particularly useful in pediatrics when anesthetizing lacerations for suture repair. Given concerns for diversion and toxicity with TAC, other forms of anesthetics such as LET (lidocaine-epinephrine-tetracaine) have largely replaced TAC.[6]

Adjuvants

The use of local anesthetics is limited by its duration of action and the dose-dependent adverse effects.[14] Prolongation of local anesthetic peripheral nerve blocks can be achieved by utilizing catheter-based techniques. However, these can post challenges, such as catheter displacement and potential for

increased infection risk.[15] An alternative is to use adjuvants to prolong the effect of local anesthetics and limit the cumulative dose requirements of the local anesthetic, thus improving the efficacy of perineural blocks and decreasing local anesthetic toxicity (Table 8-3).[14] Many adjuvants have been used in adult medicine, but all are off-label use and no adjuvant has been approved by the FDA for prolongation of peripheral nerve blocks.[15]

Table 8-3

Local Anesthetic Adjuncts

Class	Drug	Route	Adverse Effects
Opioid	Morphine	Intrathecal and epidural	Respiratory depression (early and late), nausea, vomiting, pruritus, urinary retention
Opioid	Fentanyl	Intrathecal and epidural	Same as for morphine, but decreased severity
Opioid	Sufentanil	Intrathecal and epidural	Sedation, bradycardia, and hypotension
Opioid	Hydromorphone	Intrathecal and epidural	Preferred in patients with renal insufficiency rather than morphine
Partial opioid agonist	Buprenorphine	Intrathecal and epidural	
Weak opioid with sodium and potassium channel blocking actions and serotonin and norepinephrine reuptake inhibition	Tramadol	Intrathecal and epidural	
Sympathomimetic	Epinephrine	Intrathecal and epidural	Tachycardia, hypertension
Alpha-2 adrenoreceptor antagonists	Clonidine	Intrathecal, epidural, and peripheral nerve blocks	Sedation, bradycardia, and hypotension
Alpha-2 adrenoreceptor antagonists	Dexmedetomidine	Intrathecal, epidural, and peripheral nerve blocks	Hypotension and bradycardia
Steroid	Dexamethasone	Intrathecal, epidural, and peripheral nerve blocks	
Benzodiazepine	Midazolam	Intrathecal and epidural	
Anticholinesterase inhibitor	Neostigmine	Intrathecal and epidural	Nausea, vomiting, bradycardia, agitation, restlessness
N-methyl-d-aspartate (NMDA) receptor antagonist	Ketamine	Intrathecal and epidural	Psychotomimetic sequelae (hallucinations, drowsiness, nausea)
NMDA receptor antagonist and inhibitor of voltage-gated calcium channel	Magnesium sulfate	Intrathecal and epidural	Bradycardia, hypotension, sedation, headache, disorientation

Various drugs have been used as adjuncts, including opioids, epinephrine, α_2-adrenergic antagonists, steroids, anti-inflammatory drugs, midazolam, ketamine, magnesium sulfate, and neostigmine.[14]

Opioids are the most frequently used local anesthetic adjuvant.[14] They potentiate antinociception of local anesthetics by G protein–coupled receptor mechanisms by causing hyperpolarization of the afferent sensory neurons.[14]

Preservative free morphine has been used extensively in neuraxial blocks across all age groups.[14] Morphine is hydrophilic, which results in a cephalad spread leading to an increased area of analgesia.

Epinephrine is one of the oldest additives to local anesthetic solutions.[14] It is believed to prolong the duration by its vasoconstrictive properties that prevent systemic reabsorption of local anesthetics.[15] It is useful for detecting intravascular injections of presumed epidural catheters.[14,15] However, epinephrine has not been shown to prolong peripheral nerve blocks, so it is not recommended for this use.[15]

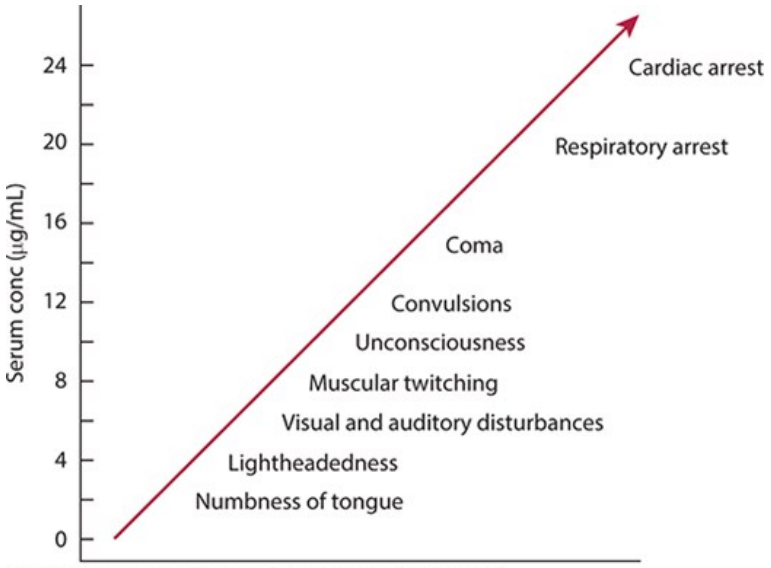
Toxicity

Systemic toxicity to local anesthetics can occur with overdose of local anesthetics or with accidental intravascular injection. The primary effects seen are central nervous system (CNS) and cardiovascular changes.

In addition to the specific effects on the central nervous and cardiovascular systems discussed next, hypercapnia, acidosis, and hypoxia have further untoward effects on these systems. The hypercapnia and acidosis that may occur with local anesthetic toxicity lead to potentiation of the negative chronotropic and inotropic actions in cardiac tissue while it leads to increased free drug and thus the amount available to the CNS with resulting exacerbation of CNS toxicity.

Figure 8-3

Local anesthetic toxicity symptoms based on serum concentration. (Adapted with permission, from Hoffman RS, Howland M, Lewin NA, Nelson LS, *Goldfrank LR. eds. Goldfrank's Toxicologic Emergencies*, 10th ed. 2015. https://accesspharmacy.mhmedical.com. Copyright © McGraw Hill LLC. All rights reserved.)



Central Nervous System Toxicity

Often the first symptoms of local anesthetic toxicity are in the CNS system and may be vague such as a sense of feeling light-headed or dizzy. Tinnitus may also be present as an early sign. It is important to note that these early findings can be difficult to assess in infants and small children, as they may be unable to verbalize what they are experiencing. This makes it important to watch for objective signs of CNS toxicity that might occur. These signs include muscle twitches and tremors and may progress to generalized seizure activity. Following this period of excitement, CNS depression may occur and lead to

respiratory failure.

Cardiovascular Toxicity

In addition to CNS effects, local anesthetic toxicity also directly and indirectly affects the cardiovascular system. Local anesthetics work to decrease the rate of depolarization in the ventricular muscle by decreasing the rate of depolarization in the fast conducting Purkinje fibers.[16]

Local anesthetics also produce negative inotropic action of the cardiac muscle. They can also lead to vasodilation of peripheral vasculature in high concentrations. Cocaine is the one exception to this in that it exerts a vasoconstrictor effect at all doses via inhibition of norepinephrine uptake and thus causing neurogenic vasoconstriction.[6]

As briefly discussed above, special attention should be given to bupivacaine's cardiovascular toxicity. Discussion of this is important, as reversal of cardiovascular collapse from bupivacaine is particularly difficult to reverse. The dose of bupivacaine required to produce irreversible cardiovascular collapse is closer to the dose necessary to produce CNS toxicity compared to lidocaine where the difference between the doses required to produce irreversible cardiovascular collapse is significantly more than that required to produce CNS toxicity.[17]

Treatment of Local Anesthetic Toxicity

It is imperative if local anesthetics are being utilized that one knows how to treat local anesthetic toxicity. Treatment is based on two things—supportive care (including resuscitation) and intralipid. Intralipid 20% at 1.5 mL/kg should be initiated immediately if a patient develops cardiovascular compromise secondary to local anesthetic toxicity. Beyond this, one should be prepared to administer an infusion of 0.25 mL/kg/min for 10 minutes following the initial bolus. Additional supportive care with basic life support (BLS), advanced cardiac life support (ACLS), and resuscitation drugs should be used as necessary. Use of lidocaine to treat arrhythmias related to local anesthetic toxicity is of course not recommended (Figure 8-3).

Methemoglobinemia

Methemoglobinemia is a unique side effect that can occur with the use of the local anesthetic prilocaine. This occurs when hepatic metabolism of prilocaine leads to production of *O*-toluidine, which in turn oxidizes hemoglobin to methemoglobin. As noted earlier, although EMLA contains prilocaine it has been shown to generally be safe in term newborns. Although it is generally considered safe, there are reports of methemoglobinemia following use of EMLA in infants.[18]

Direct Nerve Toxicity

Neurologic injury after peripheral nerve blocks is multifactorial. At the site of injection, nerve damage can be due to needle injury, hematoma, or local anesthetic toxicity.[3] Utilization of nerve stimulation techniques does not prevent intraneural injections, and intraneural injections do not necessarily result in injury. Injection inside the epineurium with low initial pressures (<5 psi) maintains normal neurologic function. Initial injection pressures less than 12 psi results in return of neurologic function to baseline within 24 hours after injection. However, high injection pressures (>20 psi) intrafascicularly leads to fascicular injury, neurologic deficits, and persistent neurologic dysfunction.[19]

Needle type may also play a role. Short bevel needles less frequently produce fascicular damage than long bevel needles.[19] However, the injuries that do occur from short bevel needles are usually more severe than those from long bevel needles.[3] Additionally, orientation of the needle affects severity of injury; injuries caused by needle bevels perpendicular to the nerve fibers are more severe than those by bevels aligned parallel.[19]

Toxicity of local anesthetics themselves is time and dose dependent. Local anesthetics can induce direct nerve injury at clinical concentrations. Toxicity levels differ among local anesthetics and can be caused by the local anesthetic itself or its additives.[3]

Patient factors also contribute to nerve injury. Those with underlying nerve pathology, such as chemotherapy-related neurotoxicity or diabetic neuropathies, are more susceptible to peripheral nerve complications.[19]

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