Local Anesthetic Agents

Mechanism of Action and Pharmacology

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The mechanism of action of local anesthetic agents is to prevent the transmission of nerve impulses generated by a chemical, mechanical, or electrical stimulus that triggers an action potential.

Anatomy of a Nerve Cell

Nerve cells communicate with each other through axons, which are elongations of the cell body, and by dendrites. The cell membrane is a hydrophobic lipid bilayer that incorporates ion channels composed of lipoproteins. In contrast to the nerve cells of the central nervous system, many peripheral nerves are enveloped in myelin produced by Schwann cells. Gaps known as nodes of Ranvier, located approximately 1 mm apart in the myelin sheath, have a high concentration of Na^+ channels, facilitating saltatory transmission between sequential nodes and increasing the speed of electrical conduction along the axon.

Nerve Cell Membrane and Depolarization

The cell membrane creates a barrier between the Na^+-rich extracellular fluid and the K^+-rich intracellular fluid, creating a resting membrane potential of $^-60$ to $^-90$ mV (Fig. 93.1). There is constant movement of Na^+ ions through Na^+ channels that spontaneously open and close; active transport of Na^+ out of the cell maintains the resting membrane potential. When an appropriate stimulus of adequate magnitude opens a sufficient number of Na^+ channels, the surrounding membrane depolarizes (becomes less negative), recruiting additional channel openings—a cascade of open channels allows more Na^+ to enter the cell, with K^+ diffusing out of the cell through K^+ channels to the point that the entire membrane depolarizes, producing an all-or-nothing electrical signal (action potential) that is propagated along the axon. Once the action potential passes, an energy-dependent mechanism reestablishes the concentrations of Na^+ and of K^+, restoring the resting membrane potential.

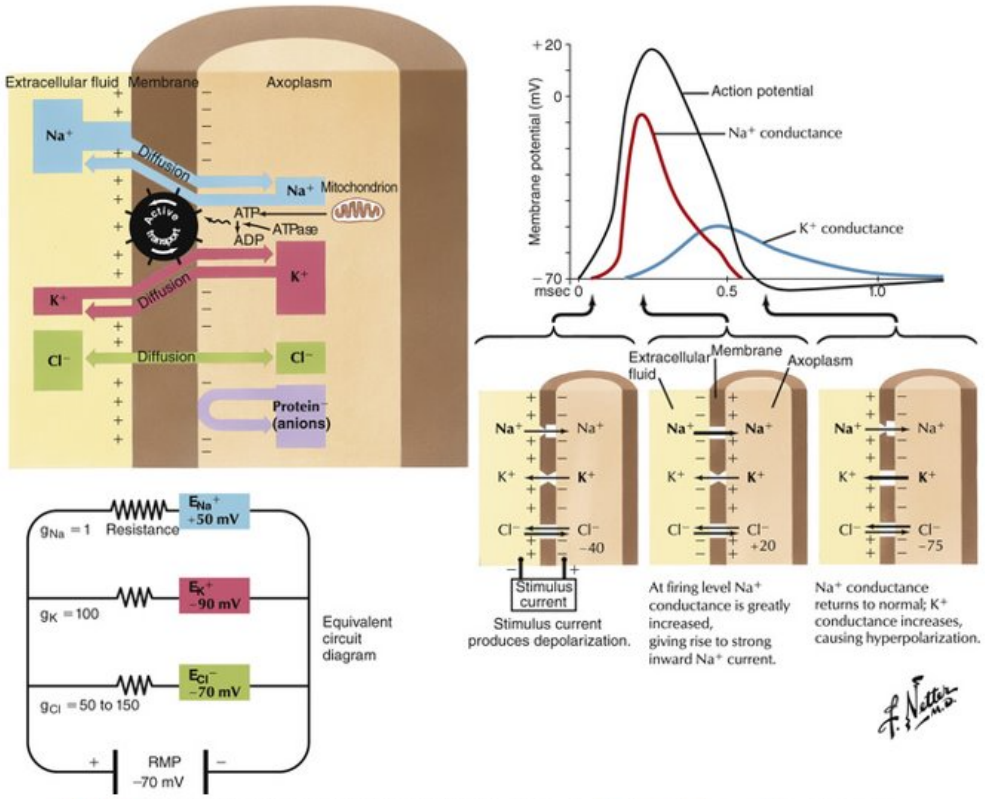

Fig. 93.1 Resting membrane and action potentials. (Netter illustration from http://www.netterimages.com. © Elsevier Inc. All rights reserved.)

Structure of Local Anesthetic Agents

Molecules of local anesthetic agents contain an aromatic lipophilic end, which is connected by an intermediate chain to a hydrophilic tertiary amine (weak base). The intermediate chain is either an amide or an ester linkage; this linkage is the basis for the two different classes of local anesthetic agents (esters and amides), which have similar mechanisms of action but different metabolic pathways. Because the nonionized form of the molecule crosses the cell membrane, compounds that are more lipophilic have a faster onset of blockade. And, because local anesthetic agents are weak bases, compounds with a pK_a close to physiologic pH will have a faster onset of blockade as more molecules remain in the nonionized state. Clearance of the drug from the site of injection and protein binding of local anesthetic agents by α_1-acid glycoprotein also affect the duration of action because it is the concentration of free drug that is available to diffuse across the membrane that determines blockade (Fig. 93.2, Table 93.1).

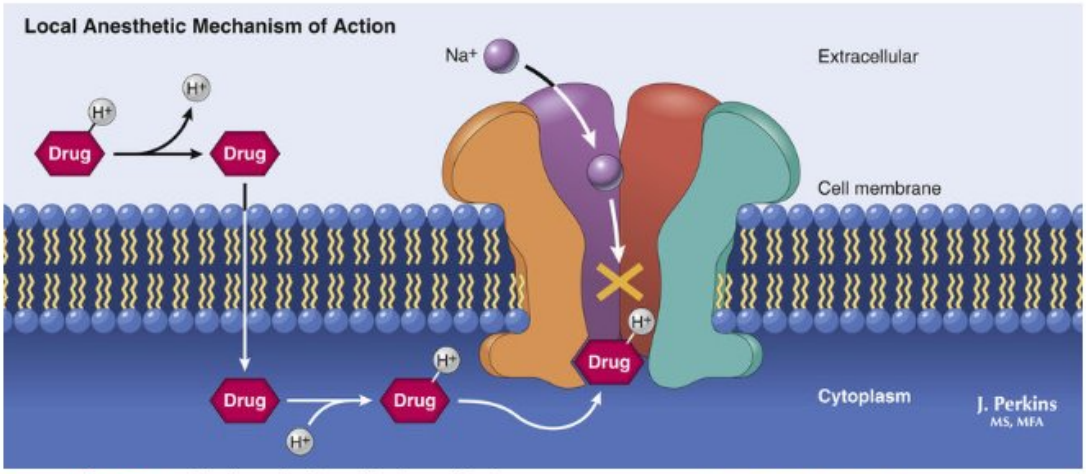

Fig. 93.2 Mechanism of action of local anesthetic agents. (Netter illustration from http://www.netterimages.com. © Elsevier Inc. All rights reserved.)

TABLE 93.1

Chemical and Physical Properties of the Most Commonly Used Local Anesthetic Drugs

Property	Lidocaine	Mepivacaine	Bupivacaine	Ropivacaine	Levobupivacaine
Molecular weight	234	246	288	274	288
pK_a	7.7	7.6	8.1	8.1	8.1
Liposolubility*	4	1	30	2.8	30
Partition coefficient	2.9	0.8	28	9	28
Protein binding (%)	65	75	95	94	95
Equipotency (%)	2	1.5	0.5	0.75	0.5

*Liposolubility of each of the local anesthetic agents, as compared with mepivacaine, (e.g., lidocaine is four times more lipid soluble than mepivacaine.

Action of Local Anesthetic Agents

Intracellular pH is typically less than 7; therefore once molecules of the local anesthetic agent cross the cell membrane, many molecules will dissociate into the ionized form of the molecule. These ions have affinity for the α subunits of the Na^+ channels. The ionized molecule of the local anesthetic agent enters a Na^+ channel from within the cell, binding with the α subunit and ultimately rendering the Na^+ channel inactive. If Na^+ cannot traverse the membrane, the cell cannot depolarize, and an action potential would not be generated. Myelinated nerves require blockade of three consecutive nodes of Ranvier to ensure impulse extinction.

Local anesthetics (LA) work by blocking sodium conductance through voltage-gated sodium channels. The cause of LA failure is unknown; however, a genetic defect has been proposed as a potential mechanism. A genetic variant that is associated with LA resistance in the gene encoding a variant form of voltage-gated sodium channel has been identified explaining a plausible reason for LA failure.

Toxicity of Local Anesthetic Agents

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High blood levels of local anesthetic (LA) agents—caused by either accidental intravascular injection or increased uptake from perivascular areas—affect organs that are dependent on sodium channels to function properly. Central nervous system (CNS) abnormalities are the first manifestation of Local Anesthetic Systemic Toxicity (LAST), whereas cardiac abnormalities result from higher concentrations of LA agents.

Prevention of LAST is dependent on injection of an appropriate volume and concentration of an LA agent, knowledge of the pharmacologic properties of these drugs, and increased vigilance for early detection of clinical symptoms.

Factors Influencing Blood Levels of Local Anesthetic Agents

The site of and route of injection (Table 94.1), the specific drug properties, the dose of the drug used, the co-administration of vasoconstricting agents, and pathways involved in the metabolism of the drug determine blood levels of an LA agent and affect not only the speed with which blood levels of LA agents rise, but also the duration of the effect and the likelihood that toxicity will develop.

TABLE 94.1

ROUTE OF ADMINISTRATION
Intravenous (fastest)
Intercostal
Caudal epidural
Lumbar epidural
Brachial plexus
Subcutaneous
Topical (slowest)

Site of Administration

Absorption of LA agents is dependent on the blood supply at the site of injection. (See Table 94.1.) Highly vascular areas are at greatest risk for uptake. Administration of LA to topical areas, especially mucosal membranes, can result in LAST.

Clinical Presentation of Systemic Toxicity

Serum concentration of LA affects the severity and type of clinical symptoms associated with LAST (Fig. 94.1).

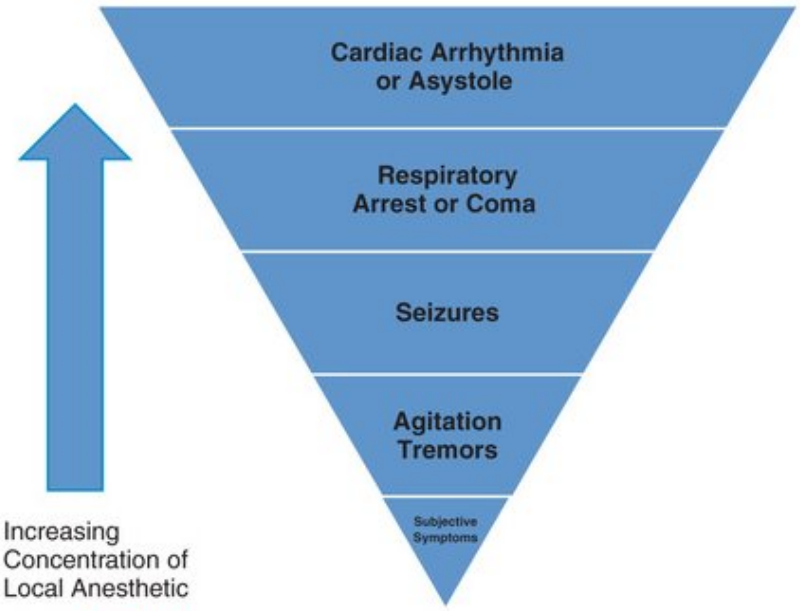

Fig. 94.1 Clinical Signs and Symptoms of Local Anesthetic Systemic Toxicity.

Central Nervous System Toxicity

The amount of CNS toxicity is proportional to the potency of the LA agent. More potent, longer-acting drugs tend to be more toxic. The initial symptoms and signs of LA-induced CNS toxicity are tinnitus, blurred vision, dizziness, tongue paresthesias, metallic taste, and perioral numbness. Excitatory phenomena (nervousness, restlessness, agitation, and muscle twitching) result from selective blockade of inhibitory pathways and often precede CNS depression, tonic-clonic seizures, and cardiopulmonary collapse. The presence of hypercarbia (secondary to CNS depression and decreased ventilatory drive) lowers the seizure threshold because the hypercarbia increases cerebral blood flow, and the associated respiratory acidosis decreases protein binding, making more free drug available.

Cardiovascular System Toxicity

All LA agents cause a dose-dependent depression in myocardial contractility and also exhibit vasodilating properties (with the exception of cocaine, a vasoconstrictor). Similar to CNS toxicity, myocardial depression is proportional to the potency of the LA agent. The use of bupivacaine has also been associated with a higher-risk profile for cardiac toxicity. When compared with lidocaine, bupivacaine is more cardiotoxic because it binds more strongly to resting or inactivated sodium channels, and bupivacaine dissociates from sodium channels during diastole more slowly than does lidocaine.

Local Anesthetic Agent Properties (Table 94.2)

TABLE 94.2

Maximum Dose and Duration of Commonly Used Local Anesthetic Agents

Agent	Maximum Dose (mg/kg)	Duration of Effect (h)
ESTERS		
Chloroprocaine	12	0.5–1
Procaine	12	0.5–1
Cocaine	3	0.5–1
Tetracaine	3	1.5–6
AMIDES		
Prilocaine	8	0.5–1
Lidocaine	4.5*	0.75–1.5
Mepivacaine	4.5*	1–2
Ropivacaine	3	1.5–8
Bupivacaine	3	1.5–8

*Maximum is 7 mg/kg if administered with epinephrine.

- Lipid Solubility: Increased lipid solubility results in greater potency. More potent LAs are more cardiotoxic.
- Protein Binding: A high degree of protein binding to alpha-1-acidic glycoprotein (AAG) and albumin results in decreasing levels of free local anesthetic systemically, relating to lesser likelihood of developing LAST.
- Volume of Distribution: A large volume of distribution (prilocaine) results in lower systemic blood levels.

Dose of Local Anesthetic Agent

The higher the concentration of the LA agent, the more likely that toxicity will occur. For example, transversus abdominis plane (TAP) blocks often require a large volume of local anesthetic, > 20 mL to ensure adequate spread, and are often performed bilaterally.

Coadministration of Vasoconstrictors

The effect of the addition of epinephrine or phenylephrine to the LA agent depends on the local blood supply at the injection site and the vasoconstrictive or dilating properties of the specific LA agent. In general, the addition of vasoconstricting agents lowers the peak blood levels and increases the time to achieve the peak blood levels of LA agents.

Metabolism

Absorption and delivery to the site of metabolism (for amides, the liver; for esters, the plasma) is necessary for LA metabolism to occur. For example, chloroprocaine is metabolized by plasma cholinesterase. Because of its short plasma half-life, episodes of reported LAST events are usually very brief, lasting less than 40 seconds.

Neural Toxicity

The use of chloroprocaine has been implicated in prolonged sensory and motor deficits in some patients. Studies have shown that although chloroprocaine itself is not neurotoxic, large amounts of chloroprocaine in the presence of sodium bisulfite and a low pH may cause neurotoxicity. Lidocaine and other LA agents also may cause neurotoxicity when administered in high doses.

Methemoglobinemia

Prilocaine is metabolized in the liver to *o*-toluidine, which oxidizes hemoglobin to methemoglobin. In general, doses of about 600 mg of prilocaine are required before clinically significant methemoglobinemia occurs. Methemoglobinemia makes pulse oximetry inaccurate, with a plateau occurring such that the O_2 saturation does not decrease below 84% to 86%, regardless of true oxygenation and even if methemoglobin comprises > 35% of the total hemoglobin. Methemoglobinemia may be treated by intravenous administration of methylene blue, 1 mg/kg.

Diagnosis, Prevention, and Treatment of Toxic Reactions

Most toxic reactions to LA agents can be prevented through safe performance of neural blockade, including careful selection of the dose and concentration of the LA agent. Use of a test dose and incremental injections with intermittent aspiration decrease the risk of systemic toxicity. Patients should be closely monitored for signs of intravascular injection (i.e., increased blood pressure and heart rate in the presence of epinephrine) or signs/symptoms of CNS toxicity.

Treatment of toxic reactions because of LA agents is similar to the management of other medical emergencies, focusing on ensuring adequate airway, breathing, and circulation. Once an airway is established, 100% O_2 should be administered. Hypoxia and hypercarbia must be avoided. If convulsions occur, a small amount of a benzodiazepine will rapidly terminate the seizure without causing cardiovascular compromise. Should intubation be required to secure the airway, succinylcholine may be administered. Although the tonic-clonic motions are inhibited in a patient given a neuromuscular blocking agent, seizure activity will still be present on an electroencephalographic tracing.

Certain modifications to advanced cardiac life support (ACLS) should be considered when treating LAST.

1. 1. Ventricular arrhythmias should be treated with amiodarone instead of lidocaine.
2. 2. Avoid vasopressin as it is associated with adverse outcomes in LAST.
3. 3. Reduce epinephrine dose to < 1 mcg IV.

Additionally, a 20% lipid emulsion should be administered (1.5 mL/kg bolus over 1 minute followed by a continuous infusion at 0.25 mL/kg/min for 10–60 min) because lipid emulsions have been associated with rapid recovery from LA toxicity. Although propofol is formulated in a lipid emulsion, the formulation is only 10% lipid; therefore propofol should not be used as a

substitute for lipid emulsion in this circumstance because the lipid content is too low to provide benefit and the cardiovascular suppression associated with the use of propofol may worsen the ability to resuscitate the patient. In some cases, patients have been placed on cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) until cardiac toxicity resolves.

Though most patients require only sustained cardiopulmonary resuscitation, repeated cardioversion may be necessary and high doses of epinephrine are often required for circulatory support.

Lipid Emulsion

There are several theories for the mechanism action for lipid emulsion therapy, but positive results may be multifactorial. The prevailing current theory is that the lipid binds the LA and removes it from effective circulation. Lipid emulsion therapy can sometimes cause aberrant lab values in routine blood testing.

Cauda Equina Syndrome

Prolonged neurologic injury with motor paralysis and sensory changes (including pain) is a rare complication that occurs when LA agents are used to induce spinal anesthesia. Although preservatives or other contaminants administered with the LA agent have been cited as the cause of this complication, neural toxicity has been described following injection of high concentrations and doses of certain LA agents, including chloroprocaine and lidocaine, independent of the preservative used. A number of cases were reported in the 1990s after the use of microcatheters for continuous spinal anesthesia with high-dose lidocaine, presumably because catheter placement allowed a high concentration of the drug to accumulate near sacral nerve roots.

Transient Neurologic Symptoms

Lidocaine is not often used in spinal anesthesia because of its association with transient neurologic symptoms. Severe pain radiating down both legs is the most commonly described symptom. Associated factors include surgical position (specifically lithotomy), early ambulation, and obesity. This poses a special problem when spinal anesthesia is chosen for short procedures because there are few alternatives for outpatient regional anesthesia. Alternatives to lidocaine include procaine, mepivacaine (which has also been associated with transient neurologic syndrome), very low dose lidocaine (25 mg) with fentanyl (25 µg), and very low dose bupivacaine (4–7 mg) with fentanyl (10–25 µg). Recently, bisulfite-free chloroprocaine has seen a rebirth in use for spinal anesthesia considering the faster return to ambulation and shorter times to meet hospital discharge criteria as compared with low-dose, but still longer-acting, bupivacaine. Thus chloroprocaine perhaps may be the best-suited LA for outpatient spinal anesthesia.

Special Populations

Pregnancy

AAG and albumin are reduced during pregnancy, which increases the free fraction of LA in pregnant patients. Additionally, increased cardiac output and epidural venous engorgement will increase absorption.

Infants

Low AAG levels and immature hepatic clearance increase risk of LAST in infants.

Liposuction

When liposuction is performed, large amounts of dilute LA agent are used, and, therefore, the total dose of LA agent administered may be quite high. The American Academy of Dermatology has published guidelines for the performance of liposuction that recommend a maximum safe dose of lidocaine of 55 mg/kg. Because the absorption of lidocaine can be delayed in adipose tissue, toxicity is more likely to occur between 6 and 12 h after the procedure, rather than immediately after the procedure.

Suggested Readings

American Society of Regional Anesthesia. *Checklist for Treatment of Local Anesthetic Toxicity*. https://www.asra.com/advisory-guidelines/article/3/checklist-for-treatment-of-local-anesthetic-systemic-toxicity.

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Local anesthetic: Transient neurologic symptoms

Definition

Lidocaine was first used as a spinal anesthetic in 1948. In 1991, case reports of cauda equina syndrome began to appear following the use of 5% lidocaine through microcatheters. Two years later, in 1993, transient neurologic symptoms (TNS), was described. TNS is a painful condition of the buttocks and thighs with possible radiation to the lower extermities, beginning as soon as a few hours after spinal anesthesia and lasting as long as ten days. Pain can be mild to severe. However, unlike in cauda equina syndrome, TNS isexclusively a pain syndrome – there is no bowel or bladder dysfunction, and neurologic, MRI , and electrophysiologic examinations are normal.

All local anesthetics can cause TNS. The incidence of TNS following lidocaine is 1:7 (13%). The relative risk of TNS when using lidocaine (versus bupivacaine, mepivacaine, prilocaine, or procaine) is 4.35, based on an analysis of 14 studies including 1347 patients. However, mepivacaine risk is about equal to lidocaine, thus the relative risk of lidocaine/mepivacaine is 7x that of bupivacaine, prilocaine, and procaine. Of note, none of the patients in this study reported permanent neurologic deficits.

Transient Neurologic Symptoms (TNS)

- Incidence: one in seven lidocaine/mepivacaine intrathecal administrations (7-fold less for bupivacaine, prilocaine, and procaine)
- Associations: all local anesthetics
- Timing: few hours to ~ 1 day, lasting up to 10 days
- Symptoms: exclusively pain in buttocks, thighs, legs, no dysfunction

Lidocaine is often chosen for neuraxial anesthesia because it has rapid onset, dense blockade, and short duration of action. However, it is also unique in its propensity to cause a phenomenon known as transient neurologic symptoms (TNS). TNS is characterized by pain in the buttocks and legs that develops within a few hours and up to 24 hours after anesthesia. Symptoms typically do not last beyond 2 days. It is important to note that although lidocaine is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine, and procaine, these drugs are less suitable for ambulatory

patients due to their prolonged action. Mepivacaine results in TNS at a similar rate as lidocaine. 2-chloroprocaine (which fell out of favor, but seems to be making a comeback) does not and therefore may be a good alternative.

Epinephrine: effect on LA duration

Basic, Clinical Sciences: Anesthesia Procedures, Methods, and Techniques

Vasoconstrictors, such as epinephrine, can be added to local anesthetics. The addition of epinephrine causes multiple effects. Blood vessel constriction causes decreased blood flow to the site of drug administration or infiltration, leading to reduced systemic absorption of LAs, lower systemic blood levels, and thus reduced risk of LA toxicity. Additionally, administration with epinephrine results in increased intraneural concentration of LAs as reduced systemic absorption allows more local anesthetic to enter into the nerve membrane and remain for a longer period of time. This results in improved depth and increased duration of action of most LAs. The increased duration of action is only partially explained by decreased blood flow to the area, as the alpha-adrenergic effects of epinephrine will wear off prior to anesthetic effect. The extent of prolongation in duration of anesthesia is also dependent on the site of injection and the local anesthetic used for the block. Shorter-duration LAs, such as lidocaine, have significantly longer duration of action when combined with epinephrine compared to LAs such as bupivacaine which have a more modest prolongation of nerve block.

Epinephrine can also be added as a marker for inadvertent intravascular injection and to help decrease bleeding at the site of administration. Norepinephrine and phenylephrine have also been used for their vasoconstrictive properties, but have not been shown to be superior to epinephrine.

Sources

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