CHAPTER 16

Local Anesthetics

KEY CONCEPTS

1. Voltage-gated sodium (Na) channels are membrane-associated proteins that comprise one large α subunit, through which Na ions pass, and one or two smaller β subunits. Na channels exist in (at least) three states—resting (nonconducting), open (conducting), and inactivated (nonconducting). Local anesthetics bind and inhibit a specific region of the α subunit, preventing channel activation and the Na influx associated with membrane depolarization.

2. The sensitivity of nerve fibers to inhibition by local anesthetics is influenced by axonal diameter, myelination, and other factors.

3. Clinical local anesthetic potency correlates with octanol solubility and the ability of the local anesthetic molecule to permeate lipid membranes. Potency is increased by adding large alkyl groups to a parent molecule. There is no clinical measurement of local anesthetic potency that is analogous to the minimum alveolar concentration (MAC) of inhalation anesthetics.

4. Onset of action depends on many factors, including lipid solubility and the relative concentration of the nonionized, more lipid-soluble free-base form (B) and the ionized, more water-soluble form (BH^+), expressed by the pK_a. The pK_a is the pH at which there is an equal fraction of ionized and nonionized drug. Less potent, less lipid-soluble agents (eg, lidocaine or mepivacaine) generally have a faster onset than more potent, more lipid-soluble agents (eg, ropivacaine or bupivacaine).

5. Duration of action correlates with potency and lipid solubility. Highly lipid-soluble local anesthetics have a longer duration of action, presumably because they more slowly diffuse from a lipid-rich environment to the aqueous bloodstream.

6. In regional anesthesia, local anesthetics are typically applied close to their

intended site of action; thus, their pharmacokinetic profiles in blood are important determinants of elimination and toxicity and have very little to do with the duration of their desired clinical effect.

7. The rates of local anesthetic systemic absorption and the rise of local anesthetic concentrations in blood are related to the vascularity of the site of injection and generally follow this rank order: intravenous (or intraarterial) > tracheal > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous.

8. Ester local anesthetics are metabolized predominantly by pseudocholinesterase. Amide local anesthetics are metabolized (N-dealkylation and hydroxylation) by microsomal P-450 enzymes in the liver.

9. In awake patients, rising local anesthetic concentrations in the central nervous system produce the premonitory signs of local anesthetic intoxication.

10. Major cardiovascular toxicity usually requires about three times the local anesthetic concentration in blood as that required to produce seizures.

11. Unintended intravascular injection of bupivacaine during regional anesthesia may produce severe cardiovascular toxicity, including left ventricular depression, atrioventricular heart block, and life-threatening arrhythmias such as ventricular tachycardia and fibrillation.

12. True hypersensitivity reactions (due to IgG or IgE antibodies) to local anesthetics —as distinct from systemic toxicity caused by excessive plasma concentrations —are uncommon. Esters appear more likely to induce an allergic reaction, especially if the compound is a derivative (eg, procaine or benzocaine) of p-aminobenzoic acid, a known allergen.

Local and regional anesthesia and analgesia techniques depend on a group of drugs—local anesthetics—that transiently inhibit some or all of sensory, motor, or autonomic nerve function when the drugs are applied near neural tissue. This chapter describes the mechanism of action, structure–activity relationships, and the clinical pharmacology of local anesthetic drugs. The more commonly used regional anesthetic techniques are presented elsewhere (see Chapters 45 and 46).

MECHANISMS OF LOCAL ANESTHETIC ACTION

Neurons (and all other living cells) maintain a resting membrane potential of –60 to –70

mV. The electrogenic, energy-consuming sodium–potassium pump (Na^+-K^+-ATPase) couples the transport of three sodium (Na) ions out of the cell for every two potassium (K) ions it moves into the cell. This creates concentration gradients that favor the movement of K ions from an intracellular to an extracellular location and the movement of Na ions in the opposite direction. The cell membrane is normally much more "leaky" to K ions than to Na ions, so a relative excess of negatively charged ions (anions) accumulates intracellularly. The combined effects of Na^+-K^+-ATPase and K ion leak account for the negative resting membrane potential.

Excitable cells (eg, neurons or myocytes) have the unusual capability of generating **action potentials**. Membrane-associated, voltage-gated Na channels in peripheral nerve axons can produce and transmit membrane depolarizations following chemical, mechanical, or electrical stimuli. Activation of voltage-gated Na channels causes a very brief (roughly 1 ms) change in the conformation of the channels, allowing an influx of Na ions and generating an action potential (**Figure 16–1**). The increase in Na permeability causes temporary depolarization of the membrane potential to +35 mV. The Na current is brief and terminated by the inactivation of voltage-gated Na channels, which do not conduct Na ions. When there is no Na ion flux, the membrane returns to its resting potential. When a stimulus is sufficient to depolarize a patch of membrane, the signal can be transmitted as a wave of depolarization along the nerve membrane (an impulse). Baseline concentration gradients are maintained by the sodium–potassium pump, and only a minuscule number of Na ions pass into the cell during an action potential.

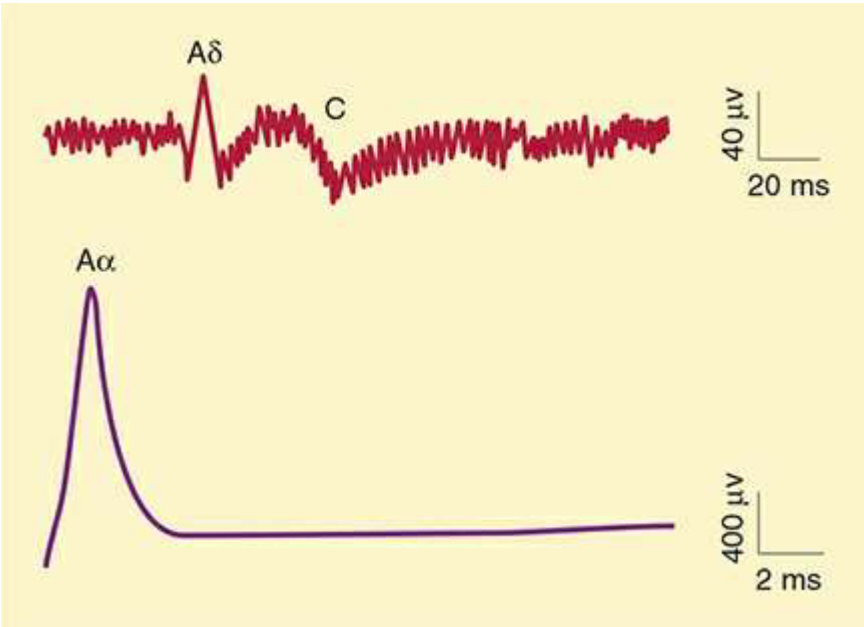


FIGURE 16–1 Compound Aα, Aδ, and C fiber action potentials recorded after supramaximal stimulation of a rat sciatic nerve. Note the differing time scale of the recordings. In peripheral nerves, Aδ and C fibers have much slower conduction velocities, and their compound action potentials are longer and of less amplitude when compared with those

from Aα fibers. (Reproduced with permission from Butterworth JF 4th, Strichartz GR. The alpha2-adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers, Anesth Analg. 1993 Feb;76(2):295-301.)

1 The previously mentioned voltage-gated Na channels are membrane-associated proteins comprising one large α subunit, through which Na ions pass, and one or two smaller β subunits. Na channels exist in (at least) three states—resting (nonconducting), open (conducting), and inactivated (nonconducting) (**Figure 16–2**). When local anesthetics bind a specific region of the α subunit, they prevent channel activation and Na influx through the individual channels. Local anesthetic binding to Na channels does not alter the resting membrane potential. With increasing local anesthetic concentrations, an increasing fraction of the Na channels in the membrane bind a local anesthetic molecule and cannot conduct Na ions. As a consequence of more channels binding a local anesthetic, the threshold for excitation and impulse conduction in the nerve increases, the rate of rise and the magnitude of the action potential decreases, and impulse conduction velocity slows. At great enough local anesthetic concentrations (when a sufficient fraction of Na channels has bound a local anesthetic), action potentials can no longer be generated, and impulse propagation is abolished. Local anesthetics have a greater affinity for the Na channel in the open or inactivated state than in the resting state. Depolarizations lead to open and inactivated channels; therefore, depolarization favors local anesthetic binding. The fraction of Na channels that bind a local anesthetic increases with frequent depolarization (eg, during trains of impulses). This phenomenon is termed use-dependent block. Put another way, local anesthetic inhibition of Na channels is both voltage (membrane potential) and frequency dependent. Local anesthetic binding is greater when nerve fibers are frequently depolarizing than with infrequent depolarizations.

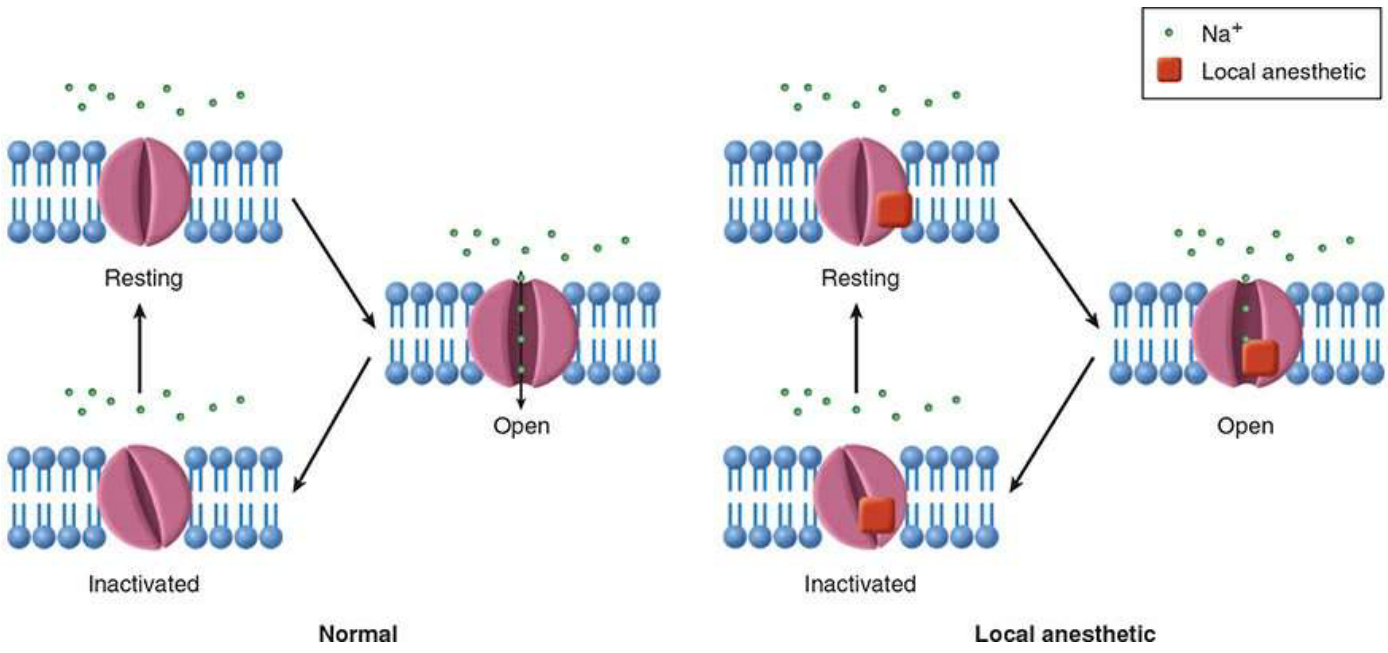


FIGURE 16–2 Voltage-gated sodium (Na_V) channels exist in at least three states—resting, open (activated), and inactivated. Resting Na_V channels activate and open when they are depolarized, briefly allowing Na ions to pass into the cell down their concentration gradient, then rapidly inactivate. Inactivated Na_V channels return to the resting state as the cell membrane repolarizes. In the figure, Na ions are shown on the extracellular side of the cell membrane. Extracellular Na ions conduct only through open Na_V channels that have not bound a local anesthetic molecule. The Na_V channel binding site for local anesthetics is nearer to the cytoplasmic than the extracellular side of the channel.

Local anesthetics may also bind and inhibit calcium (Ca), K, transient receptor potential vanilloid-1 (TRPV1), and many other channels and receptors. Conversely, other classes of drugs, notably tricyclic antidepressants (amitriptyline), meperidine, volatile anesthetics, Ca channel blockers, α_2-receptor agonists, and nerve toxins may also inhibit Na channels. Tetrodotoxin and saxitoxin are poisons that specifically bind Na channels at a site on the exterior of the plasma membrane. Human studies are underway with similar toxins to determine whether they might provide effective, prolonged analgesia.

2 Sensitivity of nerve fibers to inhibition by local anesthetics is influenced by axonal diameter, myelination, and other factors. Table 16–1 lists the most commonly used classification for nerve fibers. In comparing nerve fibers of the same type (myelinated versus unmyelinated), smaller diameter associates with increased sensitivity to local anesthetics and with slower conduction velocity. Thus, larger, faster-conducting Aα fibers are less sensitive to local anesthetics than smaller, slower-conducting Aδ fibers. Larger unmyelinated fibers are less sensitive than smaller unmyelinated fibers. On the other hand, small unmyelinated C fibers are relatively resistant to inhibition by local anesthetics as compared with relatively larger myelinated fibers. In a human peripheral nerve, the onset of local anesthetic inhibition generally follows this sequence: autonomic before sensory before motor. But at steady state, if sensory anesthesia is present, usually all modalities are inhibited.

TABLE 16–1 Nerve fiber classification.[1]

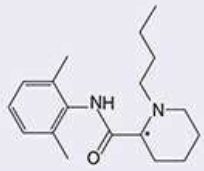
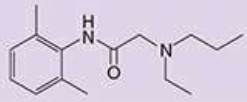
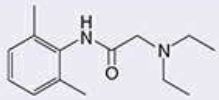
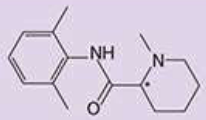
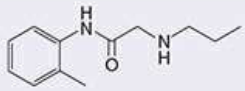
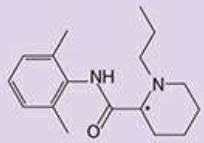
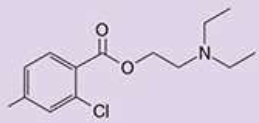
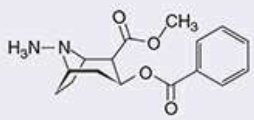
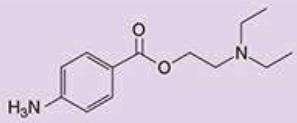
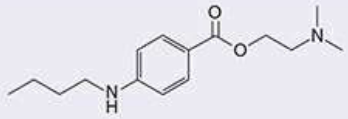
Fiber Type	Modality Served	Diameter (mm)	Conduction (m/s)	Myelinated?
Aα	Motor efferent	12–20	70–120	Yes
Aα	Proprioception	12–20	70–120	Yes
Aβ	Touch, pressure	5–12	30–70	Yes
Aγ	Motor efferent (muscle spindle)	3–6	15–30	Yes
Aδ	Pain Temperature Touch	2–5	12–30	Yes
B	Preganglionic autonomic fibers	<3	3–14	Some
C Dorsal root	Pain Temperature	0.4–1.2	0.5–2	No
C Sympathetic	Postganglionic sympathetic fibers	0.3–1.3	0.7–2.3	No

[1]An alternative numerical system is sometimes used to classify sensory fibers.

STRUCTURE–ACTIVITY RELATIONSHIPS

Local anesthetics consist of a lipophilic group (usually an aromatic benzene ring) separated from a hydrophilic group (usually a tertiary amine) by an intermediate chain that includes an ester or amide linkage. The nature of the intermediate chain is the basis of the classification of local anesthetics as either esters or amides (Table 16–2). Articaine, a popular local anesthetic for dentistry in several European countries, is an amide, but it contains a thiophene ring rather than a benzene ring. Local anesthetics are weak bases that at physiological pH usually carry a positive charge at the tertiary amine group. Physicochemical properties of local anesthetics depend on the substitutions in the aromatic ring, the type of linkage in the intermediate chain, and the alkyl groups attached to the amine nitrogen.

TABLE 16–2 Physicochemical properties of local anesthetics.

Generic (Proprietary)	Structure	Relative Lipid Solubility of Unchanged Local Anesthetic	pK_a	Protein Binding (%)
Amides				
Bupivacaine (Marcaine, Sensorcaine)		8	8.2	96
Etidocaine (Duranest)		16	8.1	94
Lidocaine (Xylocaine)		1	8.2	64
Mepivacaine (Carbocaine)		0.3	7.9	78
Prilocaine (Citanest)		0.4	8.0	53
Ropivacaine (Naropin)		2.5	8.2	94
Esters				
Chloroprocaine (Nesacaine)		2.3	9.1	NA[1]
Cocaine		NA	8.7	91
Procaine (Novocaine)		0.3	9.1	NA
Tetracaine (Pontocaine)		12	8.6	76

*Carbon atom responsible for optical isomerism.

[1]NA, not available.

3 Clinical local anesthetic potency correlates with octanol solubility and the ability of the local anesthetic molecule to permeate lipid membranes. Potency is increased by adding large alkyl groups to a parent molecule (compare tetracaine with procaine or bupivacaine with mepivacaine). There is no clinical measurement of local anesthetic potency that is analogous to the minimum alveolar concentration (MAC) of inhalation anesthetics. The minimum concentration of local anesthetic that will block nerve impulse conduction is affected by several factors, including fiber size, type, and myelination; pH (an acidic environment antagonizes clinical nerve block); frequency of nerve stimulation; and electrolyte concentrations (hypokalemia and hypercalcemia antagonize blockade).

4 Onset of local anesthetic action depends on many factors, including lipid solubility and the relative concentration of the nonionized, more lipid-soluble free-base form (B) and the ionized water-soluble form (BH^+), expressed by the pK_a. The pK_a is the pH at which there is an equal fraction of ionized and nonionized drug. Less potent, less lipid-soluble agents (eg, lidocaine or mepivacaine) generally have a faster onset than more potent, more lipid-soluble agents (eg, ropivacaine or bupivacaine).

Local anesthetics with a pK_a closest to physiological pH will have (at physiological pH) a greater fraction of nonionized base that more readily permeates the nerve cell membrane, generally facilitating a more rapid onset of action. It is the lipid-soluble free-base form that more readily diffuses across the neural sheath (epineurium) and through the nerve membrane. Curiously, once the local anesthetic molecule gains access to the cytoplasmic side of the Na channel, it is the charged cation (rather than the nonionized base) that more avidly binds the Na channel. For instance, the pK_a of lidocaine exceeds physiological pH. Thus, at physiological pH (7.40), more than half the lidocaine will exist as the charged cation form (BH^+).

The importance of pK_a in understanding differences among local anesthetics is often overstated. It has been asserted that the onset of action of local anesthetics directly correlates with pK_a. This is not supported by data; in fact, the agent of fastest onset (2-chloroprocaine) has the greatest pK_a of all clinically used agents. Other factors, such as ease of diffusion through connective tissue, can affect the onset of action in vivo. Moreover, not all local anesthetics exist in a charged form (eg, benzocaine).

The importance of the ionized and nonionized forms has many clinical implications for those agents that exist in both forms. Local anesthetic solutions are prepared commercially as water-soluble hydrochloride salts (pH 6–7). Because epinephrine is unstable in alkaline environments, commercially formulated local anesthetic solutions containing epinephrine are generally more acidic (pH 4–5) than the comparable "plain" solutions lacking epinephrine. As a direct consequence, these commercially formulated,

epinephrine-containing preparations may have a lower fraction of free base and a slower onset than solutions to which the epinephrine is added by the clinician immediately prior to use. Similarly, the extracellular base-to-cation ratio is decreased and onset is delayed when local anesthetics are injected into acidic (eg, infected) tissues. Some researchers have found that alkalinization of local anesthetic solutions (particularly commercially prepared, epinephrine-containing ones) by the addition of sodium bicarbonate (eg, 1 mL 8.4% sodium bicarbonate per 10 mL local anesthetic) speeds the onset and improves the quality of the block, presumably by increasing the fraction of free-base local anesthetic. Interestingly, alkalinization also decreases pain during subcutaneous infiltration.

5 Duration of action correlates with potency and lipid solubility. Highly lipid-soluble local anesthetics have a longer duration of action, presumably because they more slowly diffuse from a lipid-rich environment to the aqueous bloodstream. Lipid solubility of local anesthetics is correlated with plasma protein binding. In blood, local anesthetics are mostly bound by α_1-acid glycoprotein and, to a lesser extent, to albumin. Sustained-release systems using liposomes or microspheres can significantly prolong local anesthetic duration of action. However, the clinical superiority of liposomal bupivacaine relative to aqueous bupivacaine is currently controversial.

Differential block of sensory but not motor function would be desirable. Unfortunately, only bupivacaine and ropivacaine display some clinically useful selectivity (mostly during the onset and offset of block) for sensory nerves; however, the concentrations required for surgical anesthesia almost always result in some motor blockade.

CLINICAL PHARMACOLOGY

Pharmacokinetics

6 In regional anesthesia, local anesthetics are typically applied close to their intended site of action; thus, their pharmacokinetic profiles in blood are important determinants of elimination and toxicity and have very little to do with the duration of their desired clinical effect.

A. Absorption

Absorption after topical application depends on the site. Most mucous membranes (eg, tracheal or oropharyngeal mucosa) provide a minimal barrier to local anesthetic penetration, leading to a rapid onset of action. Intact skin, on the other hand, requires topical application of an increased concentration of lipid-soluble local anesthetic base

to ensure permeation and analgesia. EMLA™ (Eutectic Mixture of Local Anesthetics) cream was formulated to overcome the obstacles presented by intact skin. It consists of a mixture of lidocaine and prilocaine bases in an emulsion. Depth of analgesia (usually <0.5 cm), duration of action (usually <2 h), and amount of drug absorbed depend on application time, dermal blood flow, and total dose administered. Typically, 1 to 2 g of cream is applied per 10-cm^2 area of skin. Dermal analgesia sufficient for inserting an intravenous catheter requires about 1 h under an occlusive dressing. EMLA cream should not be used on mucous membranes, broken skin, infants younger than 1 month of age, or patients with a contraindication to either lidocaine or prilocaine.

Systemic absorption of injected local anesthetics depends on blood flow, which is determined by the following factors.

1. Site of injection—

7 The rates of local anesthetic systemic absorption and rise of local anesthetic concentrations in blood are related to the vascularity of the site of injection and generally follow this rank order: intravenous (or intraarterial) > tracheal (transmucosal) > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous.

2. Presence of additives—

The addition of epinephrine causes vasoconstriction at the site of administration, leading to some or all of the following: reduced peak local anesthetic concentration in blood, facilitated neuronal uptake, enhanced quality of analgesia, prolonged duration of analgesia, and reduced toxic side effects. Vasoconstrictors have more pronounced effects on shorter-acting than on longer-acting agents. For example, the addition of epinephrine to lidocaine usually extends the duration of anesthesia by at least 50%, but epinephrine has a limited effect on the duration of bupivacaine peripheral nerve blocks. Epinephrine and clonidine may also augment analgesia through the activation of α_2-adrenergic receptors. Coadministration of dexamethasone or other steroids with local anesthetics can prolong blocks by up to 50%. Mixtures of local anesthetics (eg, ropivacaine and mepivacaine) produce nerve blocks with onset and duration that are intermediate between the two parent compounds.

3. Local anesthetic agent—

More lipid-soluble local anesthetics that are highly tissue bound are also more slowly absorbed than less lipid-soluble agents. The agents also vary in their intrinsic vasodilator properties.

B. Distribution

Distribution depends on organ uptake, which is determined by the following factors.

1. Tissue perfusion—

The highly perfused organs (brain, lung, liver, kidney, and heart) are responsible for the initial rapid removal of local anesthetics from blood, which is followed by a slower redistribution to a wider range of tissues. In particular, the lung extracts significant amounts of local anesthetic during the "first pass"; consequently, patients with right-to-left cardiac shunts are more susceptible to toxic side effects of lidocaine injected as an antiarrhythmic agent.

2. Tissue/blood partition coefficient—
Increasing lipid solubility is associated with greater plasma protein binding and also greater tissue uptake of local anesthetics from an aqueous compartment.

3. Tissue mass—
Muscle provides the greatest reservoir for the distribution of local anesthetic agents in the bloodstream because of its large mass.

C. Biotransformation and Excretion

The biotransformation and excretion of local anesthetics are defined by their chemical structure. For all compounds, very little nonmetabolized local anesthetic is excreted by the kidneys.

1. Esters—
8 Ester local anesthetics are predominantly metabolized by pseudocholinesterase (also termed butyrylcholinesterase). Ester hydrolysis is rapid, and the water-soluble metabolites are excreted in the urine. Procaine and benzocaine are metabolized to p-aminobenzoic acid (PABA), which has been associated with rare anaphylactic reactions. Patients with genetically deficient pseudocholinesterase would theoretically be at increased risk for toxic side effects from ester local anesthetics, as metabolism is slower, but clinical evidence for this is lacking, most likely because alternative metabolic pathways are available in the liver. In contrast to other ester anesthetics, cocaine is primarily metabolized (ester hydrolysis) in the liver.

2. Amides—
Amide local anesthetics are metabolized (N-dealkylation and hydroxylation) by microsomal P-450 enzymes in the liver. The rate of amide metabolism depends on the specific agent (prilocaine > lidocaine > mepivacaine > ropivacaine > bupivacaine) but is consistently slower than ester hydrolysis of ester local anesthetics. Decreases in hepatic function (eg, with cirrhosis) or in liver blood flow (eg, congestive heart failure, β-blockers, or H_2-receptor blockers) will reduce the rate of amide metabolism and potentially predispose patients to have greater blood concentrations and a greater risk of systemic toxicity. Water-soluble local anesthetic metabolites are dependent on renal clearance.

Prilocaine is the only local anesthetic that is metabolized to o-toluidine, which produces methemoglobinemia in a dose-dependent fashion. Classical teaching was that a defined dose of prilocaine (in the range of 10 mg/kg) must be exceeded to produce clinically consequential methemoglobinemia; however, recent studies have shown that younger, healthier patients develop medically important methemoglobinemia after lower doses of prilocaine (and at lower doses than needed in older, sicker patients). Prilocaine currently has limited use in North America but is more commonly used in other regions. **Benzocaine, a common ingredient in topical local anesthetic sprays, can also cause dangerous levels of methemoglobinemia**. For this reason, many hospitals no longer permit benzocaine spray during endoscopic procedures. Treatment of medically important methemoglobinemia includes intravenous methylene blue (1–2 mg/kg of a 1% solution over 5 min). Methylene blue reduces methemoglobin (Fe^{3+}) to hemoglobin (Fe^{2+}).

Effects on Organ Systems

Because voltage-gated Na channels underlie action potentials in neurons throughout the body as well as impulse generation and conduction in the heart, it is not surprising that increased circulating concentrations of local anesthetics could produce systemic toxicity. Although organ system effects are discussed for these drugs as a group, individual drugs differ.

Potency at most toxic side effects correlates with local anesthetic potency at nerve blocks. "Maximum safe doses" are listed in Table 16–3, but it must be recognized that the maximum safe dose depends on the patient, the specific nerve block, the rate of injection, and a long list of other factors. In other words, tables of purported maximal safe doses are nearly nonsensical. Mixtures of local anesthetics should be considered to have additive toxic effects; therefore, injecting a solution combining 50% of a toxic dose of lidocaine and 50% of a toxic dose of bupivacaine likely will produce toxic effects.

TABLE 16–3 Clinical use of local anesthetic agents.

Agent	Techniques	Concentrations Available	Maximum Dose (mg/kg)	Typical Duration of Nerve Blocks[1]
Esters				
Benzocaine	Topical[2]	20%	NA[3]	NA
Chloroprocaine	Epidural, infiltration, peripheral nerve block, spinal[4]	1%, 2%, 3%	12	Short
Cocaine	Topical	4%, 10%	3	NA
Procaine	Spinal, local infiltration	1%, 2%, 10%	12	Short
Tetracaine (amethocaine)	Spinal, topical (eye)	0.2%, 0.3%, 0.5%, 1%, 2%	3	Long
Amides				
Bupivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.25%, 0.5%, 0.75%	3	Long
Lidocaine (lignocaine)	Epidural, spinal, infiltration, peripheral nerve block, intravenous regional, topical	0.5%, 1%, 1.5%, 2%, 4%, 5%	4.5 7 (with epinephrine)	Medium
Mepivacaine	Epidural, infiltration, peripheral nerve block, spinal	1%, 1.5%, 2%, 3%	4.5 7 (with epinephrine)	Medium
Prilocaine	EMLA (topical), epidural, intravenous regional (outside North America)	0.5%, 2%, 3%, 4%	8	Medium
Ropivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.2%, 0.5%, 0.75%, 1%	3	Long

[1]Wide variation depending on concentration, location, technique, and whether combined with a vasoconstrictor (epinephrine). Generally, the shortest duration is with spinal anesthesia and the longest with peripheral nerve blocks.

[2]No longer recommended for topical anesthesia.

[3]NA, not applicable or not defined.

[4]Recent literature describes this agent for short-duration spinal anesthesia.

A. Neurological

9 The central nervous system is vulnerable to local anesthetic systemic toxicity (LAST); fortunately, there are premonitory signs and symptoms of increasing local anesthetic concentrations in blood in awake patients. Such symptoms include circumoral numbness, tongue paresthesia, dizziness, tinnitus, blurred vision, and a feeling of impending doom. Such signs include restlessness, agitation, nervousness, and garrulousness. Muscle twitching precedes tonic–clonic seizures. Still higher blood concentrations may produce central nervous system depression (eg, coma and respiratory arrest). The excitatory reactions are thought to be the result of selective blockade of inhibitory pathways. Potent, highly lipid-soluble local anesthetics produce seizures at lower blood concentrations than less potent agents. Benzodiazepines, propofol, and hyperventilation raise the threshold of local anesthetic-induced seizures.

Both respiratory and metabolic acidosis reduce the seizure threshold. Propofol (0.5–2 mg/kg) quickly and reliably terminates seizure activity (as do comparable doses of benzodiazepines or barbiturates). Some clinicians use intravenous lipid to terminate local anesthetic-induced seizures (see below). Maintaining a clear airway with adequate ventilation and oxygenation is most important.

Infused local anesthetics have a variety of actions. Lidocaine infusions are used to inhibit ventricular arrhythmias. Systemically administered local anesthetics such as lidocaine (1.5 mg/kg) can decrease cerebral blood flow and attenuate the rise in intracranial pressure that may accompany intubation in patients with decreased intracranial compliance. Infusions of lidocaine and procaine have been used to supplement general anesthetic techniques, as they are capable of reducing the MAC of volatile anesthetics by up to 40%. Infusions of lidocaine inhibit inflammation and reduce postoperative pain. In some studies, infused lidocaine reduced postoperative opioid requirements sufficiently to reduce length of stay after surgery.

Cocaine stimulates the central nervous system and at moderate doses usually causes a sense of euphoria. An overdose is heralded by restlessness, emesis, tremors, convulsions, arrhythmias, respiratory failure, and cardiac arrest.

In the past, unintentional injection of large volumes of chloroprocaine into the subarachnoid space (during attempts at epidural anesthesia) produced total spinal anesthesia, marked hypotension, and prolonged neurological deficits. The cause of this neural toxicity may be a combination of the low pH of chloroprocaine and a preservative, sodium bisulfite. Chloroprocaine has also been occasionally associated with unexplained severe back pain following epidural administration. Chloroprocaine is available in a preservative (bisulfite)-free formulation that has been used safely and successfully for many thousands of brief spinal anesthetics, providing strong evidence that the compound itself has minimal direct neurotoxicity

Administration of 5% lidocaine has been associated with neurotoxicity (cauda equina syndrome) after use in continuous spinal anesthesia. This may be due to pooling of drug around the cauda equina. In animal experiments, undiluted 5% lidocaine can produce permanent neuronal damage. Transient neurological symptoms (including dysesthesias, burning pain, and aching in the lower extremities and buttocks) have been reported following spinal anesthesia with a variety of local anesthetic agents, but most commonly after use of lidocaine 5% for male outpatients undergoing surgery in the lithotomy position. These symptoms (sometimes referred to as “radicular irritation”) typically resolve within 4 weeks. Many clinicians have abandoned lidocaine and substituted 2-chloroprocaine, mepivacaine, or small doses of bupivacaine for spinal anesthesia in the hope of avoiding these transient symptoms.

B. Respiratory

Lidocaine depresses the ventilatory response to low PaO_2 (hypoxic drive). Apnea can result from phrenic and intercostal nerve paralysis (eg, from "high" spinals) or depression of the medullary respiratory center following direct exposure to local anesthetic agents (eg, after retrobulbar blocks; see Chapter 36). However, apnea after administration of a "high" spinal or epidural anesthetic is nearly always the result of hypotension and brain ischemia rather than phrenic block. Local anesthetics relax bronchial smooth muscle. Intravenous lidocaine (1.5 mg/kg) may block the reflex bronchoconstriction sometimes associated with intubation.

C. Cardiovascular

10 Signs of cardiovascular stimulation (tachycardia and hypertension) may occur with local anesthetic concentrations that produce central nervous system excitation or from injection or absorption of epinephrine (often compounded with local anesthetics). Myocardial contractility and conduction velocity are also depressed at higher blood concentrations. All local anesthetics depress myocardial automaticity (spontaneous phase IV depolarization). These effects result from direct actions on cardiac muscle membrane (ie, cardiac Na channel inhibition) and in intact organisms from inhibition of the autonomic nervous system. At low concentrations, all local anesthetics inhibit nitric oxide, causing vasoconstriction. All local anesthetics except cocaine produce smooth muscle relaxation and arterial vasodilation at higher concentrations, including arteriolar vasodilation. At increased blood concentrations, the combination of arrhythmias, heart block, depression of ventricular contractility, and hypotension may culminate in cardiac arrest. Major cardiovascular toxicity usually requires about three times the local anesthetic concentration in blood as that required to produce seizures. Cardiac arrhythmias or circulatory collapse are the usual presenting signs of cardiac LAST during general anesthesia.

The hypertension associated with laryngoscopy and intubation is often attenuated by intravenous administration of lidocaine (1.5 mg/kg) 1–3 min prior to instrumentation. Overdoses of lidocaine can lead to marked left ventricular contractile dysfunction.

11 Unintended intravascular injection of bupivacaine during regional anesthesia may produce severe cardiovascular LAST, including left ventricular depression, atrioventricular heart block, and life-threatening arrhythmias such as ventricular tachycardia and fibrillation. Pregnancy, hypoxemia, and respiratory acidosis are predisposing risk factors. Young children may also be at increased risk of toxicity. Multiple studies have demonstrated that bupivacaine is associated with more pronounced changes in conduction and a greater risk of arrhythmias than comparable doses of lidocaine. Mepivacaine, ropivacaine, and bupivacaine each have a chiral carbon and therefore can exist in either of two optical isomers (enantiomers). The R(+)

optical isomer of bupivacaine blocks more avidly and dissociates more slowly from cardiac Na channels than does the S(–) optical isomer (levobupivacaine or ropivacaine). Resuscitation from bupivacaine-induced cardiac toxicity is often difficult and resistant to standard resuscitation drugs. Multiple clinical reports suggest that bolus administration of nutritional lipid emulsions at 1.5 mL/kg can resuscitate bupivacaine-intoxicated patients who do not respond to standard therapy. We advocate that lipid be a first-line treatment for cardiovascular LAST. We are concerned that case reports indicate persisting delayed use of this nearly risk-free treatment despite an American Society of Regional Anesthesia and Pain Medicine (ASRA) guideline on LAST being available in print, online, and in a mobile app.

Ropivacaine shares many physicochemical properties with bupivacaine. Onset time and duration of action are similar, but ropivacaine produces less motor block when injected at the same volume and concentration as bupivacaine (which may reflect an overall lower potency as compared with bupivacaine). Ropivacaine appears to have a greater therapeutic index than racemic bupivacaine. This improved safety profile likely reflects its formulation as a pure S(–) isomer—that is, having no R(+) isomer—as opposed to racemic bupivacaine. Levobupivacaine, the S(–) isomer of bupivacaine, was reported to have less risk of LAST than the racemic mixture, but it is no longer available in the United States.

Cocaine's cardiovascular reactions are unlike those of any other local anesthetic. Cocaine inhibits the normal reuptake of norepinephrine by adrenergic nerve terminals, thereby potentiating the effects of adrenergic stimulation. Cardiovascular responses to cocaine include hypertension and ventricular ectopy. Initial treatment of systemic cocaine toxicity should include benzodiazepines to reduce the central stimulation. Cocaine-induced arrhythmias have been successfully treated with α-adrenergic antagonists and amiodarone. Cocaine produces vasoconstriction when applied topically and is a useful agent to reduce pain and bleeding related to nasal intubation in awake patients.

D. Immunological

True hypersensitivity reactions (due to IgG or IgE antibodies) to local anesthetics —as distinct from LAST caused by excessive plasma concentrations—are uncommon. Esters appear more likely to induce an allergic reaction, especially if the compound is a derivative (eg, procaine or benzocaine) of PABA, a known allergen. Commercial multidose preparations of amides often contain **methylparaben**, which has a chemical structure vaguely similar to that of PABA. As a consequence, generations of anesthesiologists have speculated whether this preservative may be responsible for most of the apparent allergic responses to amide agents, particularly when skin testing fails to confirm true allergy to the local anesthetic.

E. Musculoskeletal

When directly injected into skeletal muscle either intentionally (eg, trigger-point injection treatment of myofascial pain) or unintentionally, local anesthetics are mildly myotoxic. Regeneration usually occurs within 4 weeks after the injection. Compounding the local anesthetic with steroid or epinephrine worsens myonecrosis. When infused into joints for prolonged periods, local anesthetics can produce severe chondromalacia.

F. Hematological

Lidocaine mildly depresses normal blood coagulation (reduced thrombosis and decreased platelet aggregation) and enhances fibrinolysis of whole blood as measured by thromboelastography. These actions could contribute to the lower incidence of thromboembolic events in patients receiving epidural anesthetics in older studies of patients not receiving prophylaxis against deep vein thrombosis.

Drug Interactions

Local anesthetics potentiate nondepolarizing muscle relaxant blockade in laboratory experiments, but this likely has no clinical importance.

As noted earlier, both succinylcholine and ester local anesthetics depend on pseudocholinesterase for metabolism. There is no evidence that this potential competition between ester local anesthetics and succinylcholine for the enzyme has any clinical importance. Dibucaine, an amide local anesthetic, inhibits pseudocholinesterase, and the extent of inhibition by dibucaine defines one form of genetically abnormal pseudocholinesterases (see Chapter 11). Pseudocholinesterase inhibitors (eg, organophosphate poisons) can prolong the metabolism of ester local anesthetics (see Table 11–2).

As noted earlier, drugs that decrease hepatic blood flow (eg, H_2-receptor blockers and β-blockers) decrease amide local anesthetic clearance. Opioids potentiate analgesia produced by epidural and spinal local anesthetics. Similarly, α_2-adrenergic agonists (eg, clonidine) potentiate local anesthetic analgesia produced after epidural or peripheral nerve block injections. Epidural chloroprocaine may interfere with the analgesic actions of neuraxial morphine, notably after cesarean delivery.

CASE DISCUSSION

Local Anesthetic Overdose

An 18-year-old woman in the active stage of labor requests an epidural anesthetic. Immediately following injection of 2 mL and 5 mL test doses of 1.5%

lidocaine with 1:200,000 epinephrine through the epidural catheter, the patient reports lip numbness and becomes very apprehensive. Her heart rate has increased from 85 to 105 beats/min.

What is your presumptive diagnosis?

Circumoral numbness and apprehension immediately following administration of lidocaine suggest an intravascular injection of local anesthetic. Abrupt tachycardia strongly suggests intravascular injection of epinephrine. Typically, these symptoms and signs after relatively small test doses will not be followed by a seizure.

What measures should be immediately undertaken?

The patient should receive supplemental oxygen. She should be closely observed for a possible (but unlikely) seizure and be reassured that the symptoms and signs will soon lapse.

What treatment should be initiated for a generalized seizure?

The laboring patient is always considered to be at increased risk for aspiration (see Chapter 41); therefore, the airway should be protected by immediate administration of succinylcholine and tracheal intubation (see Case Discussion, Chapter 17). The succinylcholine will eliminate tonic–clonic activity but will not address the underlying cerebral hyperexcitability. We favor administering an anticonvulsant such as midazolam (1–2 mg) or propofol (20–50 mg) with or before succinylcholine. Thus, wherever conduction anesthetics are administered, resuscitation drugs and equipment must be available just as for a general anesthetic.

What could have been expected if a large dose of bupivacaine (eg, 15 mL 0.5% bupivacaine)—instead of lidocaine—had been given intravascularly?

When administered at "comparably anesthetizing" doses, bupivacaine is more likely to produce cardiac LAST than lidocaine. Acute acidosis (nearly universal after a seizure) tends to potentiate LAST. Ventricular arrhythmias and conduction disturbances may lead to cardiac arrest and death. Cardiac Na channels more slowly unbind bupivacaine than lidocaine. Amiodarone may be given as treatment for LAST-induced ventricular tachyarrhythmias, but we favor immediate administration of lipid emulsion with the onset of seizures and most certainly at the first signs of cardiac toxicity from bupivacaine. Vasopressors may be required. We recommend incremental small (0.5-1 mcg/kg) doses of epinephrine. The reason for the apparent greater susceptibility to local anesthetic cardiotoxicity during pregnancy is unclear. Although the total dose (regardless of concentration) of local anesthetic determines toxicity, the U.S. Food and Drug Administration recommends against the use of

0.75% bupivacaine in pregnant and older adult patients, and in any case this concentration is not needed.

What could have prevented the toxic reaction described?

The risk from accidental intravascular injections during attempted epidural anesthesia is reduced by using test doses and administering the local anesthetic dose in smaller, safer aliquots ("every dose is a test dose"). Finally, one should administer only the minimum required dose for a given regional anesthetic.

SUGGESTED READINGS

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WEBSITES

This website provides up-to-date information about the use of lipid for rescue from local anesthetic toxicity. http://www.lipidrescue.org

The American Society of Regional Anesthesia and Pain Medicine (ASRA) website provides access to all ASRA guidelines (all of which are related to local anesthetics, regional anesthesia, or pain medicine). http://www.asra.com