CHAPTER 16

Local Anesthetics

KEY CONCEPTS

1. Sodium (Na) channels are membrane-bound proteins that are composed of one large α subunit, through which Na ions pass, and one or two smaller β subunits. Voltage-gated Na channels exist in (at least) three states—resting (nonconducting), open (conducting), and inactivated (nonconducting). Local anesthetics bind a specific region of the α subunit and inhibit voltage-gated Na channels, preventing channel activation and the Na influx associated with membrane depolarization.
2. Sensitivity of nerve fibers to inhibition by local anesthetics is determined by axonal diameter, myelination, and other anatomic and physiological factors.
3. Potency correlates with octanol solubility, which in turn reflects 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 measurement of local anesthetic potency that is analogous to the minimum alveolar concentration of inhalation anesthetics.
4. Onset of action depends on many factors, including lipid solubility and the relative concentration of the nonionized lipid-soluble form (B) and the ionized water-soluble form (BH^+), expressed by the pK_a. The pK_a is the pH at which the fraction of ionized and nonionized drug is equal. Less potent, less lipid-soluble agents generally have a faster onset than more potent, more lipid-soluble agents.
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 injected or applied very close to their intended site of action; thus their pharmacokinetic profiles are much more important determinants of elimination and toxicity than of their desired clinical effect.
7. The rate of systemic absorption is related to the vascularity of the site of injection: intravenous (or intraarterial) > tracheal > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous.
8. Ester local anesthetics are predominantly metabolized by pseudocholinesterase. Amide local anesthetics are metabolized (N-dealkylation and hydroxylation) by microsomal P-450 enzymes in the liver.
9. The central nervous system is vulnerable to local anesthetic toxicity and is the site of premonitory signs of rising blood concentrations in awake patients.

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

11 Unintentional 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 to local anesthetic agents—as distinct from systemic toxicity caused by excessive plasma concentration—are uncommon. Esters appear more likely to induce a true allergic reaction (due to IgG or IgE antibodies) especially if they are derivatives (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 sensory, motor, or autonomic nerve function, or a combination of these functions, when the drugs are injected or applied near neural tissue. This chapter presents the mechanism of action, structure–activity relationships, and clinical pharmacology of local anesthetic drugs. The more commonly used regional anesthetic techniques are presented in Section IV (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 by active transport and passive diffusion of ions. 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 an ionic disequilibrium (concentration gradient) that favors 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. This accounts for the negative resting potential difference (−70 mV polarization).

Unlike most other types of tissue, excitable cells (eg, neurons or cardiac myocytes) have the capability of generating **action potentials**. Membrane-bound, voltage-gated Na channels in peripheral nerve axons can produce and transmit membrane depolarizations following chemical, mechanical, or electrical stimuli. 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). Activation of voltage-gated Na channels causes a very brief (roughly 1 msec) change in the conformation of the channel, 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 is terminated by inactivation of voltage-gated Na channels, which do not conduct Na ions. Subsequently the membrane returns to its resting potential. 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.

1 Na channels are membrane-bound proteins that are composed of one large α subunit, through which Na ions pass, and one or two smaller β subunits. Voltage-gated Na channels exist in (at least) three states—resting (nonconducting), open

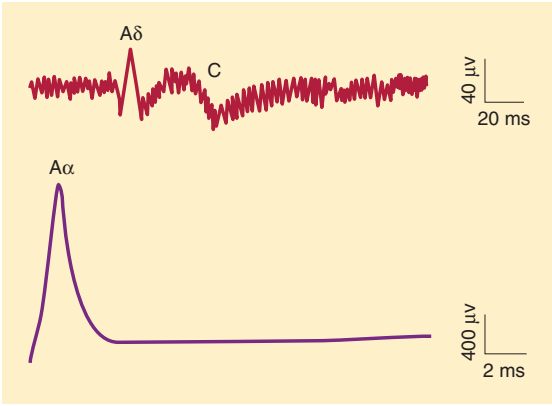


FIGURE 16–1 Compound Aα, Aδ, and C fiber action potentials recorded after supramaximal stimulation of a rat sciatic nerve. Note the differing time scale of the recordings. In peripheral nerves, Aδ and C fibers have much slower conduction velocities, and their compound action potentials are longer and of less amplitude when compared with those from Aα fibers. (Reproduced, with permission, from Butterworth JF 4th, Strichartz GR: The alpha 2-adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers. Anesth Analg 1993;76:295.)

(conducting), and inactivated (nonconducting) (Figure 16–2). Local anesthetics bind a specific region of the α subunit and inhibit voltage-gated Na channels, preventing channel activation and inhibiting the Na influx associated with membrane depolarization. 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, impulse conduction slows, the rate of rise and the magnitude of the action potential decrease, and the threshold for excitation and impulse conduction increases progressively. At high enough local anesthetic concentrations and with a sufficient fraction of local anesthetic-bound Na channels, an action potential can no longer be generated and impulse propagation is abolished. Local anesthetics have a greater affinity for the channel in the open or inactivated state than in the resting state. Local anesthetic binding to open or inactivated channels, or both, is facilitated by depolarization. The fraction of Na channels that have bound 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 is both voltage and frequency dependent, and is greater when nerve fibers are firing rapidly than with infrequent depolarizations.

Local anesthetics may also bind and inhibit calcium (Ca), K, transient receptor potential

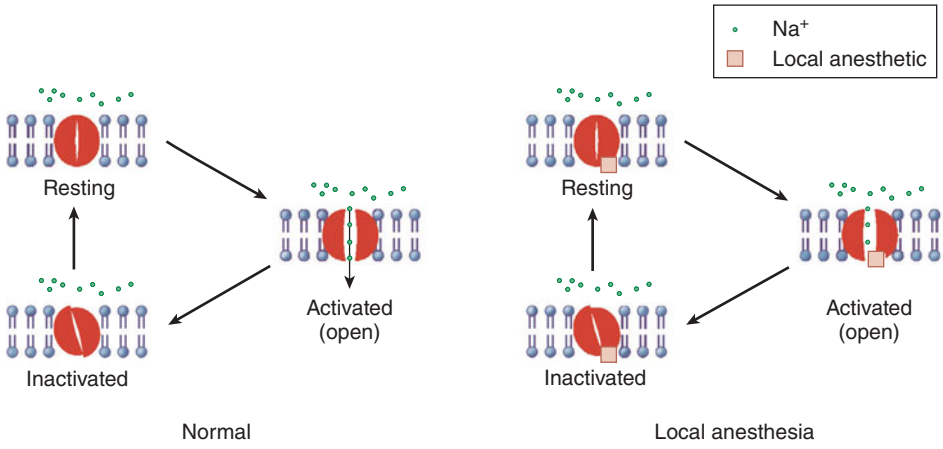


FIGURE 16–2 Voltage-gated sodium (Na) channels exist in (at least) three states—resting, activated (open), and inactivated. Note that local anesthetics bind and inhibit the voltage-gated Na channel from a site that is not directly accessible from outside the cell, interfering with the large transient Na influx associated with membrane depolarization.

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.

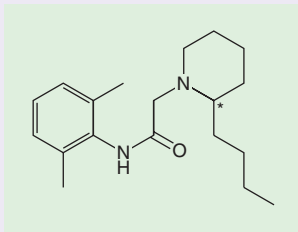
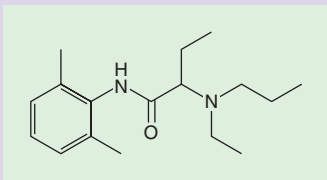
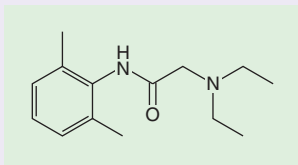
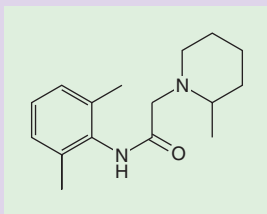
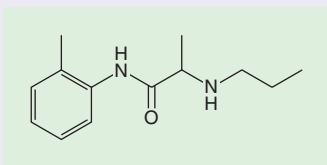
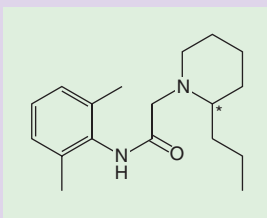
vanilloid 1 (TRPV1), and many other channels and receptors. Conversely, other classes of drugs, most notably tricyclic antidepressants (amitriptyline), meperidine, volatile anesthetics, Ca channel blockers, and ketamine, also may inhibit Na channels. Tetrodotoxin is a poison that specifically binds Na channels but at a site on the exterior of the plasma membrane. Human studies are under way with similar toxins to determine whether they might provide effective, prolonged analgesia after local infiltration.

2 Sensitivity of nerve fibers to inhibition by local anesthetics is determined by axonal diameter, myelination, and other anatomic and physiological factors. Table 16–1 lists the most commonly used classification for nerve fibers. In comparing nerve fibers of the same type, small diameter increases sensitivity to local anesthetics. Thus, larger, faster Aα fibers are less sensitive to local anesthetics than smaller, slower-conducting Aδ fibers, and 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 larger myelinated fibers. In spinal nerves local anesthetic inhibition (and conduction failure) generally follows the sequence autonomic > sensory > motor, but at steady state if sensory anesthesia is present all fibers are inhibited.

STRUCTURE–ACTIVITY RELATIONSHIPS

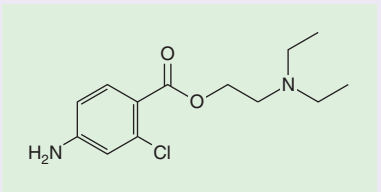
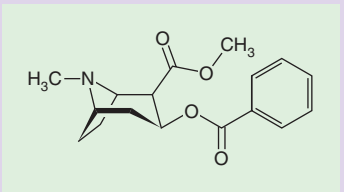
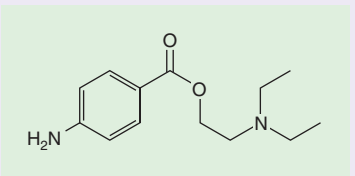
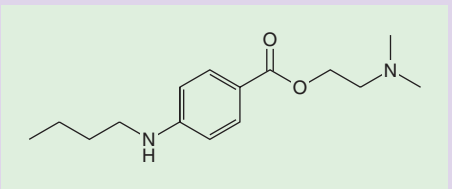
Local anesthetics consist of a lipophilic group (usually an aromatic benzene ring) separated from a hydrophilic group (usually a tertiary amine) by an intermediate chain that includes an ester or amide linkage. Articaine, the most popular local anesthetic for dentistry in several European countries,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

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

(*continued*)

TABLE 16–2 Physicochemical properties of local anesthetics. (continued)

Generic (Proprietary)	Structure	Relative Lipid Solubility of Unchanged Local Anesthetic	pK_a	Protein Binding (%)
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.

chain, and the alkyl groups attached to the amine nitrogen.

3 Potency correlates with octanol solubility, which in turn reflects 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 to procaine or bupivacaine to mepivacaine). There is no 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 (acidic pH antagonizes 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 lipid-soluble form (B) and the ionized water-soluble form (BH^+), expressed by the pK_a. The pK_a is the pH at which the fraction of ionized and nonionized drug is equal. Less potent, less lipid-soluble agents generally

have a faster onset than more potent, more lipid-soluble agents.

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 form that more readily diffuses across the neural sheath (epineurium) and passes 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^+).

It is often stated that the onset of action of local anesthetics directly correlates with pK_a. This assertion is not supported by actual 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, at least 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, epinephrine-containing, local anesthetic solutions 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 concentration of free base and a slower onset than when the epinephrine is added by the clinician at the time of use. Similarly, the extracellular base-to-cation ratio is decreased and onset is delayed when local anesthetics are injected into acidic (eg, infected) tissues. Tachyphylaxis—the decreased efficacy of repeated doses—could be partly explained by the eventual consumption of the local extracellular buffering capacity by repeat injections of the acidic local anesthetic solution, but data are lacking. 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 by increasing the amount of free base available. 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. Local anesthetics are mostly bound by α_1-acid glycoprotein and to a lesser extent to albumin. Sustained-release systems using liposomal encapsulation or microspheres for delivery of local anesthetics can significantly prolong their duration of action, but these approaches are not yet being used for prolonged anesthesia in the way that extended-duration epidural morphine is being used for single-shot, prolonged epidural analgesia.

Differential block of sensory rather than motor function would be desirable. Unfortunately, only bupivacaine and ropivacaine display *some* selectively (mostly during 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 injected or applied very close to their intended site of action; thus their pharmacokinetic profiles are much more important determinants of elimination and toxicity than of their desired clinical effect.

A. Absorption

Most mucous membranes (eg, ocular conjunctiva, tracheal mucosa) provide a minimal barrier to local

anesthetic penetration, leading to a rapid onset of action. Intact skin, on the other hand, requires a high concentration of lipid-soluble local anesthetic base to ensure permeation and analgesia. EMLA cream consists of a 1:1 mixture of 5% lidocaine and 5% prilocaine bases in an oil-in-water emulsion. Dermal analgesia sufficient for beginning an intravenous line requires a contact time of at least 1 h under an occlusive dressing. Depth of penetration (usually 3–5 mm), duration of action (usually 1–2 h), and amount of drug absorbed depend on application time, dermal blood flow, keratin thickness, and total dose administered. Typically, 1–2 g of cream is applied per 10-cm^2 area of skin, with a maximum application area of 2000 cm^2 in an adult (100 cm^2 in children weighing less than 10 kg). Split-thickness skin-graft harvesting, laser removal of portwine stains, lithotripsy, and circumcision have been successfully performed with EMLA cream. Side effects include skin blanching, erythema, and edema. EMLA cream should not be used on mucous membranes, broken skin, infants younger than 1 month of age, or patients with a predisposition to methemoglobinemia (see Biotransformation and Excretion, below).

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

7 **1. Site of injection**—The rate of systemic absorption is related to the vascularity of the site of injection: intravenous (or intraarterial) > tracheal > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous.

2. Presence of vasoconstrictors—Addition of epinephrine—or less commonly phenylephrine—causes vasoconstriction at the site of administration. The consequent decreased absorption reduces the peak local anesthetic concentration in blood, facilitates neuronal uptake, enhances the quality of analgesia, prolongs the duration of action, and limits toxic side effects. Vasoconstrictors have more pronounced effects on shorter-acting than longer-acting agents. For example, addition of epinephrine to lidocaine usually extends the duration of anesthesia by at least 50%, but epinephrine has little or no effect on the duration of bupivacaine peripheral nerve blocks. Epinephrine and clonidine can also augment analgesia through activation of α_2-adrenergic receptors.

3. Local anesthetic agent—More lipid-soluble local anesthetics that are highly tissue bound are also more slowly absorbed. 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 uptake (α phase), which is followed by a slower redistribution (β phase) to moderately perfused tissues (muscle and gut). In particular, the lung extracts significant amounts of local anesthetic; consequently, the threshold for systemic toxicity involves much lower doses following arterial injections than venous injections (and children with right-to-left 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 from an aqueous compartment.

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

C. Biotransformation and Excretion

The biotransformation and excretion of local anesthetics is defined by their chemical structure.

8 **1. Esters**—Ester local anesthetics are predominantly metabolized by pseudocholinesterase (plasma cholinesterase or butyrylcholinesterase). Ester hydrolysis is very 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 abnormal pseudocholinesterase would theoretically be at increased risk for toxic side effects, as metabolism is slower, but clinical evidence for this is lacking. Cerebrospinal fluid lacks esterase enzymes, so the termination of action of intrathecally injected ester local anesthetics, eg, tetracaine, depends on

their redistribution into the bloodstream, as it does for all other nerve blocks. In contrast to other ester anesthetics, cocaine is partially metabolized (N-methylation and ester hydrolysis) in the liver and partially excreted unchanged in the urine.

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 overall is consistently slower than ester hydrolysis of ester local anesthetics. Decreases in hepatic function (eg, cirrhosis of the liver) or liver blood flow (eg, congestive heart failure, β blockers, or H_2-receptor blockers) will reduce the metabolic rate and potentially predispose patients to having greater blood concentrations and a greater risk of systemic toxicity. Very little unmetabolized local anesthetic is excreted by the kidneys, although water-soluble 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 minimal dose of prilocaine was needed to produce clinically important methemoglobinemia (in the range of 10 mg/kg); 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 is generally not used for epidural anesthesia during labor or in larger doses in patients with limited cardiopulmonary reserve. **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 inhibition of voltage-gated Na channels from circulating local anesthetics might affect action potentials in neurons throughout the body as well as impulse generation and conduction in the heart, it is not surprising that local anesthetics in high circulating concentrations could have the propensity for 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 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, a solution containing 50% of the toxic dose of lidocaine and 50% of the toxic dose of bupivacaine if injected by accident intravenously will produce toxic effects.

A. Neurological

9 The central nervous system is vulnerable to local anesthetic toxicity and is the site of premonitory signs of rising blood concentrations in awake patients. Early symptoms include circumoral numbness, tongue paresthesia, dizziness, tinnitus, and blurred vision. Excitatory signs include restlessness, agitation, nervousness, garrulousness, and a feeling of "impending doom." Muscle twitching heralds the onset of 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 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). Maintaining a clear airway with adequate ventilation and oxygenation is of key importance.

Infused local anesthetics have a variety of actions. Systemically administered local anesthetics such as lidocaine (1.5 mg/kg) can decrease cerebral

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.

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

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. Infused lidocaine reduces postoperative opioid requirements sufficiently to reduce length of stay after colorectal or open prostate 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.

Local anesthetics temporarily inhibit neuronal function. **In the past, unintentional injection of large volumes of chloroprocaine into the subarachnoid space (during attempts at epidural anesthesia), produced total spinal anesthesia and marked hypotension, and caused prolonged**

neurological deficits. The cause of this neural toxicity may be direct neurotoxicity or a combination of the low pH of chloroprocaine and a preservative, sodium bisulfite. The latter has been replaced in some formulations by an antioxidant, a derivative of disodium ethylenediaminetetraacetic acid (EDTA). Chloroprocaine has also been occasionally associated with severe back pain following epidural administration. The etiology is unclear. Chloroprocaine is available in a preservative-free formulation, which has been used in recent studies safely and successfully for short duration, outpatient spinal anesthetics.

Administration of 5% lidocaine has been associated with neurotoxicity (cauda equina syndrome) following infusion through small-bore catheters used in continuous spinal anesthesia. This may be due to pooling of drug around the cauda equina, resulting in high concentrations and permanent neuronal damage. Animal data suggest that the extent of histological evidence of neurotoxicity following repeat intrathecal injection is lidocaine = tetracaine > bupivacaine > ropivacaine.

Transient neurological symptoms, which consist of dysesthesia, burning pain, and aching in the lower extremities and buttocks, have been reported following spinal anesthesia with a variety of local anesthetic agents, most commonly after use of lidocaine for outpatient spinal anesthesia in men undergoing surgery in the lithotomy position. These symptoms have been attributed to radicular irritation and typically resolve within 1–4 weeks. Many clinicians have substituted 2-chloroprocaine, mepivacaine, or small doses of bupivacaine for lidocaine in spinal anesthesia in the hope of avoiding these transient symptoms.

B. Respiratory

Lidocaine depresses hypoxic drive (the ventilatory response to low PaO_2). Apnea can result from phrenic and intercostal nerve paralysis or depression of the medullary respiratory center following direct exposure to local anesthetic agents (as may occur after retrobulbar blocks; see Chapter 36). Apnea after administration of a "high" spinal or epidural anesthetic is nearly always the result of hypotension, rather than phrenic block. Local anesthetics relax bronchial smooth muscle. Intravenous lidocaine (1.5 mg/kg) may be effective in blocking the reflex bronchoconstriction sometimes associated with intubation. Lidocaine (or any other inhaled agent) administered as an aerosol can lead to bronchospasm in some patients with reactive airway disease.

C. Cardiovascular

All local anesthetics depress myocardial automaticity (spontaneous phase IV depolarization). Myocardial contractility and conduction velocity are also depressed at higher concentrations. These effects result from direct cardiac muscle membrane changes (ie, cardiac Na channel blockade) and in intact organisms from inhibition of the autonomic nervous system. All local anesthetics except cocaine produce smooth muscle relaxation at higher concentrations, which may cause some degree of arteriolar vasodilation. At low concentrations all local anesthetics inhibit nitric oxide, causing vasoconstriction. 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 local anesthetic overdose during general anesthesia. Particularly in awake subjects, signs of transient cardiovascular stimulation (tachycardia and hypertension) may occur with central nervous system excitation at local anesthetic concentrations producing central nervous system toxic side effects.

Intravenous amiodarone provides effective treatment for some forms of ventricular arrhythmias. Myocardial contractility and arterial blood pressure are generally unaffected by the usual intravenous doses. The hypertension associated with laryngoscopy and intubation is attenuated in some patients by intravenous administration of lidocaine (1.5 mg/kg) 1–3 min prior to instrumentation. On the other hand, overdoses of lidocaine can lead to marked left ventricular contractile dysfunction.

11 Unintentional 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. 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 terminal arrhythmias than comparable doses of lidocaine. Mepivacaine, ropivacaine, and bupivacaine have chiral carbons 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. Resuscitation from bupivacaine-induced cardiac toxicity is often difficult and resistant to standard resuscitation drugs. Recent reports suggest that bolus administration of nutritional lipid solutions at 1.5 mL/kg can resuscitate bupivacaine-intoxicated patients who do not respond to standard therapy. 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 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, which is no longer available in the United States, was reported to have fewer cardiovascular and cerebral side effects than the racemic mixture; studies suggest its cardiovascular effects may approximate those of ropivacaine.

Cocaine's cardiovascular reactions are unlike those of any other local anesthetic. Adrenergic nerve terminals normally reabsorb norepinephrine after its release. Cocaine inhibits this reuptake, thereby potentiating the effects of adrenergic stimulation. Cardiovascular responses to cocaine include hypertension and ventricular ectopy. The latter contraindicated its use in patients anesthetized with halothane. **Cocaine-induced arrhythmias** have been successfully treated with adrenergic and Ca channel antagonists. Cocaine produces vasoconstriction when applied topically and is a useful agent to reduce pain and epistaxis related to nasal intubation in awake patients.

D. Immunological

12 True hypersensitivity reactions to local anesthetic agents—as distinct from systemic toxicity caused by excessive plasma concentration—are uncommon. Esters appear more likely to induce a true allergic reaction (due to IgG or IgE antibodies) especially if they are derivatives (eg, procaine or benzocaine) of *p*-aminobenzoic acid, 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. The signs and treatment of allergic drug reactions are discussed in Chapter 55.

E. Musculoskeletal

When directly injected into skeletal muscle (eg, trigger-point injection treatment of myofascial pain), local anesthetics are mildly myotoxic. Regeneration usually occurs 3–4 weeks after local anesthetic injection into muscle. Concomitant steroid or epinephrine injection worsens the myonecrosis.

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 effects may underlie the reduced efficacy of an epidural autologous blood patch shortly after local anesthetic administration and the lower incidence of embolic 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 the clinical importance of this observation is unknown (and probably nil).

Succinylcholine and ester local anesthetics depend on pseudocholinesterase for metabolism. Concurrent administration might conceivably increase the time that both drugs remain unmetabolized in the bloodstream. There is likely no actual clinical importance of this potential interaction.

Dibucaine, an amide local anesthetic, inhibits pseudocholinesterase, and the extent of inhibition by dibucaine defines one family of genetically abnormal pseudocholinesterases (see Chapter 11). Pseudocholinesterase inhibitors (eg, organophosphate poisons) can prolong the metabolism of ester local anesthetics (see Table 11–3).

Histamine (H_2) receptor blockers and β blockers (eg, propranolol) decrease hepatic blood flow and lidocaine clearance. Opioids potentiate epidural and spinal analgesia produced by 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 the epidural injection of 2 mL and 5 mL test doses of 2% lidocaine, the patient complains of lip numbness and becomes very apprehensive.

What is your presumptive diagnosis?

Circumoral numbness and apprehension immediately following administration of lidocaine suggest an intravascular injection. These signs will not always be followed by a seizure.

What prophylactic measures should be immediately taken?

The patient should already be receiving supplemental oxygen. She should be closely observed for a possible (but unlikely) seizure.

If symptoms progress to a generalized convulsion, what treatment should be initiated?

The laboring patient is always considered to be at risk for aspiration (see Chapter 41). Therefore, protecting the airway is an important concern. Immediate administration of succinylcholine should be followed by a rapid-sequence intubation (see Case Discussion, Chapter 17). Although the succinylcholine will eliminate tonic–clonic activity, it will not address the underlying cerebral excitability. An anticonvulsant such as midazolam (1–2 mg) or propofol (20–50 mg) should be administered with or before succinylcholine. It is clear from this sequence of events that wherever conduction anesthetics are administered, comparable resuscitation drugs and equipment must be available 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 cardiotoxic than lidocaine. Acute acidosis (nearly universal after a seizure) tends to potentiate local anesthetic toxicity. Ventricular arrhythmias and conduction disturbances may lead to cardiac arrest and death. Bupivacaine is considered a more potent cardiac Na channel inhibitor because Na channels unbind bupivacaine more slowly than lidocaine. Amiodarone should be considered the preferred alternative to lidocaine in the treatment of local anesthetic-induced ventricular tachyarrhythmias. Vasopressors may include epinephrine and vasopressin. The reason for the apparent greater susceptibility to local anesthetic cardiotoxicity during pregnancy is unclear. Although total dose (not concentration) of local anesthetic determines toxicity, the Food and

Drug Administration recommends against use of 0.75% bupivacaine in pregnant and elderly patients.

What could have prevented the toxic reaction described?

The risk from an accidental intravascular injection of local anesthetic during attempted epidural anesthesia is reduced by using test doses and administering the anesthetic dose in smaller, safer aliquots. Finally, one should administer only the minimum appropriate total dose of local anesthetic for a given regional anesthetic procedure.

SUGGESTED READING

Cousins MJ, Carr DB, Horlocker TT, Bridenbaugh PO (editors): *Cousins & Bridenbugh's Neural Blockade in Clinical Anesthesia and Pain Medicine*, 4th ed. Lippincott, Williams & Wilkins, 2009.

Hadzic A (editor): *Textbook of Regional Anesthesia and Acute Pain Management*. McGraw-Hill, 2007. Includes discussions of the selection of local anesthetic agents.

Hardman J, Limbird L, Gilman A: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 12th ed. McGraw-Hill, 2011.

Rosenblatt MA, Abel M, Fischer GW, et al: Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine–related cardiac arrest. Anesthesiology 2006;105:217-218.

Strichartz GR, Sanchez V, Arthur GR, et al: Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficients and pK_a values of clinically used drugs. Anesth Analg 1990;71:158.

WEB SITE

http://www.lipidrescue.org

This web site provides up-to-date information about the use of lipid for rescue from local anesthetic toxicity.