Chapter

10 LOCAL ANESTHETICS

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Local anesthesia can be defined as loss of sensation in a discrete region of the body caused by disruption of impulse generation or propagation. Local anesthesia can be produced by various chemical and physical means. However, in routine clinical practice, local anesthesia is produced by several compounds whose mechanism of action is similar, although they have different durations of action, and from which recovery is normally spontaneous, predictable, and complete.

HISTORY

Clinical use of local anesthetics began with cocaine in the 1880s.[1] The topically applied local anesthetic benzocaine and the injectable drugs procaine, tetracaine, and chloroprocaine were subsequently developed as adaptations of cocaine's structure as an amino ester (Figs. 10.1 and 10.2).

In 1948, lidocaine was introduced as the first member of a new class of local anesthetics, the amino amides. Advantages of the amino amides over the earlier amino esters included more stability and a reduced frequency of allergic reactions. Because of these favorable properties, lidocaine became the template for the development of a series of amino-amide anesthetics (see Fig. 10.2).

Along with lidocaine, most amino-amide local anesthetics are derived from the aromatic amine xylidine, including mepivacaine, bupivacaine, ropivacaine, and levobupivacaine. Ropivacaine and levobupivacaine share an additional distinctive characteristic: they are single enantiomers rather than racemic mixtures. They are products of a developmental strategy that takes advantage of the differential stereoselectivity of neuronal and cardiac sodium ion channels in an effort to reduce the potential for cardiac toxicity (see "Adverse Effects"). Almost all of the amides undergo biotransformation in the liver, whereas the esters undergo hydrolysis in plasma.

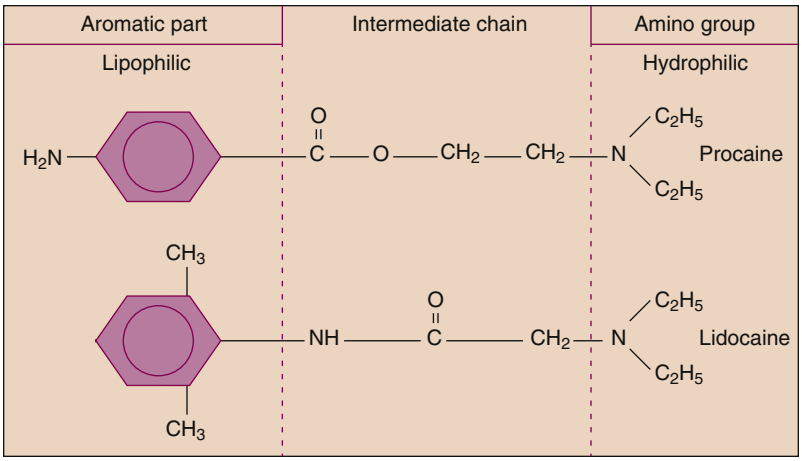

Fig. 10.1 Local anesthetics have three portions: (1) lipophilic, (2) hydrophilic, and a connecting (3) hydrocarbon chain. This figure illustrates creative ways of altering this basic structure for desired pharmacologic characteristics (duration of action, cardiovascular).

NERVE CONDUCTION

Under normal or resting circumstances, the neural membrane is characterized by a negative potential of roughly –90 mV (the potential inside the nerve fiber is negative relative to the extracellular fluid). This negative potential is created by energy-dependent outward transport of sodium and inward transport of potassium ions, combined with greater membrane permeability to potassium ions relative to sodium ions. With excitation of the nerve, there is an increase in the membrane permeability to sodium ions, causing a decrease in the transmembrane potential. If a critical potential is reached (i.e., threshold potential), there is a rapid and self-sustaining influx of sodium ions resulting in a propagating wave of depolarization, the action potential, after which the resting membrane potential is reestablished.

Nerve fibers can be classified according to fiber diameter, presence (type A and B) or absence (type C) of myelin, and function (Table 10.1). The nerve fiber diameter influences conduction velocity; a larger diameter correlates with more rapid nerve conduction. The presence of myelin also increases conduction velocity. This effect results from insulation of the axolemma from the surrounding media, forcing current to flow through periodic interruptions in the myelin sheath (i.e., nodes of Ranvier) (Fig. 10.3).

LOCAL ANESTHETIC ACTIONS ON SODIUM CHANNELS

Local anesthetics act on a wide range of molecular targets, but they exert their predominant desired clinical effects by blocking sodium ion flux through voltage-gated sodium channels. Voltage-gated sodium channels are complex transmembrane proteins comprising large alpha subunits and much smaller beta subunits[2] (Fig. 10.4).

The alpha subunits have four homologous domains arranged in a square, each composed of six transmembrane helices, and the pore lies in the center of these four domains. Beta subunits modulate electrophysiologic properties of the channel and they also have prominent roles in channel localization, binding to adhesion molecules, and connection to intracellular cytoskeletons. There are nine major subtypes of sodium channel alpha subunits in mammalian tissues and four major subtypes of beta subunits.

Different sodium channel subtypes are expressed in different tissues, at diverse developmental stages, and in a range of disease states. Sodium channel subtypes are an active area of investigation around human diseases with spontaneous pain and pain insensitivity, as targets of new analgesics, and in other areas of medicine, including cardiology and neurology.[2,3] Sodium channel subtypes will be discussed briefly again later in this chapter (see "When Local Anesthesia Fails" and "Future Local Anesthetics").

From an electrophysiologic standpoint, local anesthetics block conduction of impulses by decreasing the rate of depolarization in response to excitation, preventing achievement of the threshold potential. They do not alter the resting transmembrane potential, and they have little effect on the threshold potential.

Sodium channels cycle between resting, open, and inactive conformations. During excitation, the sodium channel moves from a resting closed state to an open activated state, with an increase in the inward flux of sodium ions and consequent depolarization. The channel transitions to an inactive state and must undergo further

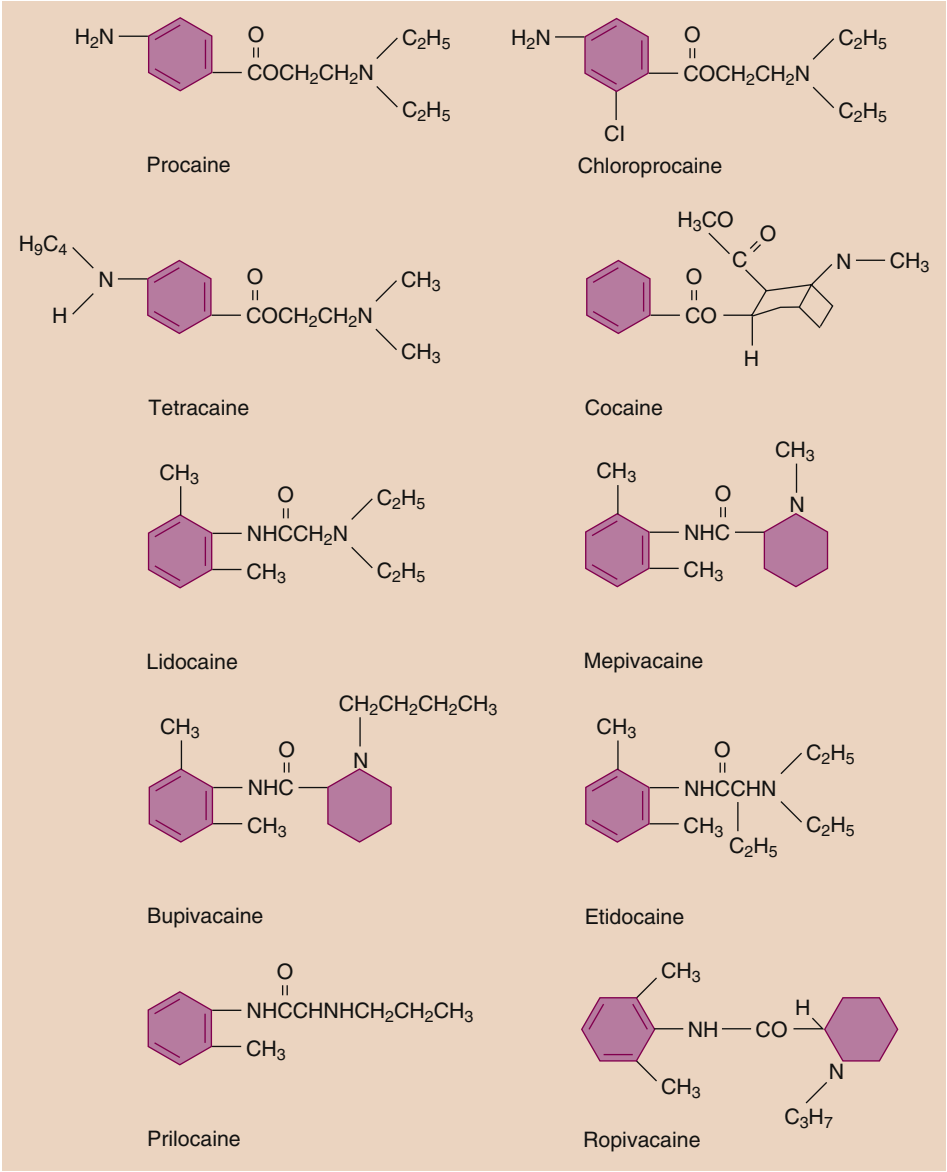

Fig. 10.2 Chemical structures of ester (i.e., procaine, chloroprocaine, tetracaine, and cocaine) and amide (i.e., lidocaine, mepivacaine, bupivacaine, etidocaine, prilocaine, and ropivacaine) local anesthetics.

Table 10.1 Classification of Nerve Fibers

Fiber				
Type	**Subtype**	**Diameter (μm)**	**Conduction Velocity (m/sec)**	**Function**
A (myelinated)	Alpha	12-20	80-120	Proprioception, large motor
	Beta	5-15	35-80	Small motor, touch, pressure
	Gamma	3-8	10-35	Muscle tone
	Delta	2-5	5-25	Pain, temperature, touch
B (myelinated)		3	5-15	Preganglionic autonomic
C (unmyelinated)		0.3-1.5	0.5-2.5	Dull pain, temperature, touch

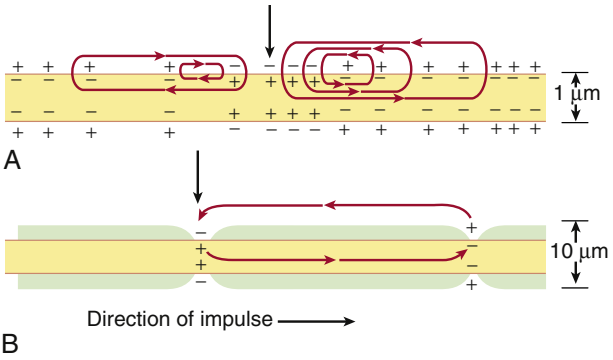

Fig. 10.3 Pattern of "local circuit currents" flowing during propagation of an impulse in a nonmyelinated C fiber's axon (A) and a myelinated axon (B). During propagation of impulses, from left to right, current entering the axon at the initial rising phase of the impulse *(large vertical arrows)* passes through the axoplasm (local circuit current) and depolarizes the adjacent membrane. Plus and minus signs adjacent to the axon membrane indicate the polarization state of the axon membrane: negative inside at rest, positive inside during active depolarization under the action potential, and less negative in regions where local circuit currents flow. This ionic current passes relatively uniformly across the nonmyelinated axon, but in the myelinated axon it is restricted to entry at the nodes of Ranvier, several of which are simultaneously depolarized during a single action potential. (From Berde CB, Strichartz GR. Local anesthetics. In Miller RD, Cohen NH, Eriksson LI, et al, eds. *Miller's Anesthesia.* 8th ed. Philadelphia: Saunders Elsevier; 2015.)

conformational change back to a resting state before it can again open in response to a wave of depolarization.

According to the modulated receptor model, local anesthetics act not by physically "plugging the pore" of the channel but rather by an allosteric mechanism; that is, by changing the relative stability and kinetics of cycling of channels through resting, open, and inactive conformations. In so doing, the fraction of channels accessible to opening and conducting inward sodium currents in response to a wave of depolarization is reduced.[4] This mechanism provides nerve blocks that are either a "use-dependent" or "frequency-dependent" type of block; that is, the block intensifies with more frequent rates of nerve firing.

pH, Net Charge, and Lipid Solubility

The predominant binding site for local anesthetics on sodium channels is near the cytoplasmic side of the plasma membrane. A major structural requirement for a molecule to be an effective local anesthetic is sufficient solubility and rapid diffusion in both hydrophilic environments (extracellular fluid, cytosol, and the headgroup region of membrane phospholipids) and in the hydrophobic environment of the lipid bilayers in plasma membranes.

The amino-amide and amino-ester local anesthetics in common clinical use achieve this aim of good solubility in both water and fat because they each contain a tertiary amine group that can rapidly convert between a protonated hydrochloride form (charged, hydrophilic) and an unprotonated base form (uncharged, hydrophobic). The charged, protonated form is the predominant active species at binding sites on sodium channels (Fig. 10.5).[5]

The relative proportion of charged and uncharged local anesthetic molecules is a function of the dissociation constant of the drug and the environmental pH. Recalling the Henderson-Hasselbalch equation, the dissociation constant (Ka) can be expressed as follows:

$$pKa = pH - \log([base]/[conjugate\ acid])$$

If the concentrations of the base and conjugate acid are equal, the latter component of the equation cancels (because log 1 = 0). Thus, the pKa provides a useful way to describe the propensity of a local anesthetic to exist in a charged or an uncharged state. The lower the pKa, the greater is the percent of un-ionized fraction at a given pH. In contrast, because the pKa values of the commonly used injectable anesthetics are between 7.6 and 8.9, less than one half of the molecules are un-ionized at physiologic pH (Table 10.2). The base forms of local anesthetics are poorly soluble in water and less stable, so they are generally marketed as water-soluble hydrochloride salts at slightly acidic pH. Bicarbonate is sometimes added to local anesthetic solutions immediately before injection to increase the un-ionized fraction in an effort to hasten the onset of anesthesia. Other conditions that lower pH, such as tissue acidosis produced by infection, inflammation, or ischemia, may likewise have a negative impact on the onset and quality of local anesthesia.

Lipid solubility of a local anesthetic affects tissue penetration, time course of uptake, potency, and duration of action. Duration of the local anesthetic action also correlates with protein binding, which likely serves to retain anesthetic within the nerve.

Degrees of anesthetic potency may be altered by the in vitro or in vivo system in which these effects are determined. For example, tetracaine is approximately 20 times more potent than bupivacaine when assessed in isolated nerve, but these drugs are nearly equipotent when assessed in vivo. Even when assessed in vivo, comparisons among local anesthetics may vary based on the specific site of application (spinal versus peripheral block) because of secondary effects such as the inherent vasoactive properties of the anesthetic.

DIFFERENTIAL LOCAL ANESTHETIC BLOCKADE

From a clinical viewpoint and from electrophysiologic measurements, local anesthesia is not an all-or-none

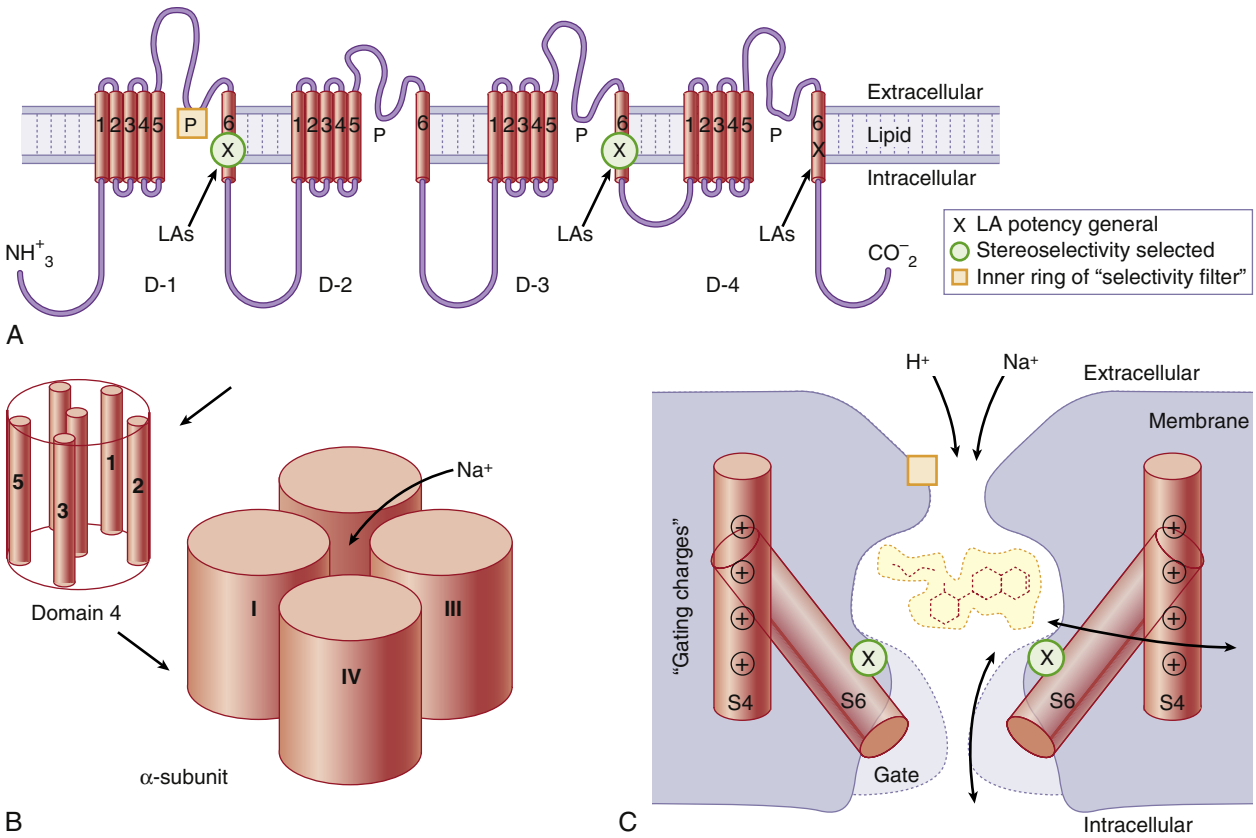

Fig. 10.4 Structural features of the Na^+ channel that determine local anesthetic (LA) interactions. (A) Consensus arrangement of the single peptide of the Na^+ channel α-subunit in a plasma membrane. Four domains with homologous sequences (D-1 through D-4) each contain six α-helical segments that span the membrane (S1 to S6). Each domain folds within itself to form one cylindrical bundle of segments, and these bundles converge to form the functional channel's quaternary structure (B). Activation gating leading to channel opening results from primary movement of the positively charged S4 segments in response to membrane depolarization (see panel C). Fast inactivation of the channel follows binding to the cytoplasmic end of the channel of part of the small loop that connects D-3 to D-4. Ions travel through an open channel along a pore defined at its narrowest dimension by the P region formed by partial membrane penetration of the four extracellular loops of protein connecting S5 and S6 in each domain. Intentional, directed mutations of different amino acids on the channel indicate residues that are involved in LA binding in the inner vestibule of the channel (X on S6 segments), at the interior regions of the ion-discriminating "selectivity filter (square on the P region), and also are known to influence stereoselectivity for phasic inhibition (circle, also on S6 segments). (C) Schematic cross section of the channel speculating on the manner in which S6 segments, forming a "gate," may realign during activation to open the channel and allow entry and departure of a bupivacaine molecule by the "hydrophilic" pathway. The closed (inactivated) channel has a more intimate association with the LA molecule, whose favored pathway for dissociation is no longer between S6 segments (the former pore) but now, much more slowly, laterally between segments and then through the membrane, the "hydrophobic" pathway. Na^+ ions entering the pore will compete with the LA for a site in the channel, and H^+ ions, which pass very slowly through the pore, can enter and leave from the extracellular opening, thereby protonating and deprotonating a bound LA molecule and thus regulating its rate of dissociation from the channel. (From Berde CB, Strichartz GR. Local anesthetics. In Miller RD, Cohen NH, Eriksson LI, et al, eds. *Miller's Anesthesia.* 8th ed. Philadelphia: Saunders Elsevier; 2015.)

phenomenon: patients experience gradations in the intensity of sensory and motor blockade that vary over time following local anesthetic injections. Clinically apparent "numbness" generally correlates with intraneural concentrations of local anesthetics but also reflects complex integration and processing of inputs in the spinal dorsal horn and at supraspinal sites in the somatosensory pathway. When compound action potentials are recorded in peripheral nerves exposed to local anesthetics in varying concentrations and lengths of nerve exposed, conduction

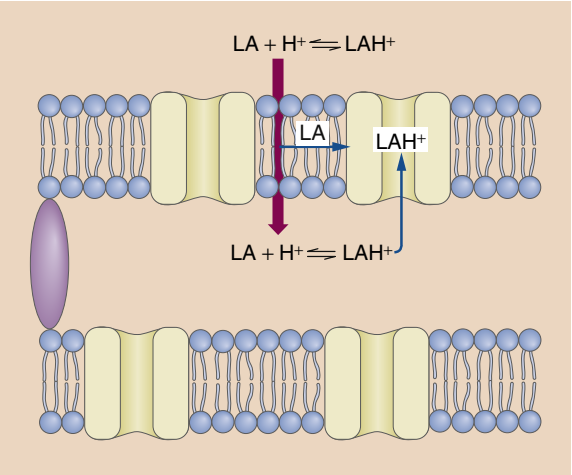

Fig. 10.5 During diffusion of local anesthetic across the nerve sheath and membrane to receptor sites within the inner vestibule of the sodium channel, only the uncharged base (LA) can penetrate the lipid membrane. After reaching the axoplasm, ionization occurs, and the charged cationic form (LAH^+) attaches to the receptor. Anesthetic may also reach the channel laterally (i.e., hydrophobic pathway). (From Covino BG, Scott DB, Lambert DH. *Handbook of Spinal Anesthesia and Analgesia.* Philadelphia: WB Saunders; 1994:7, used with permission.)

blockade is facilitated either by increasing the concentration of local anesthetic or by increasing the length of nerve exposed to more dilute concentrations. At the limit of short lengths of nerve exposed to local anesthetic, conduction blockade requires exposure of at least three successive nodes of Ranvier to prevent the action potential from "skipping over" the region of local anesthetic exposure.

Historically, the term *differential blockade* in clinical textbooks referred to the observation that infusions of dilute concentrations of local anesthetic could produce analgesia and signs of autonomic blockade with relative sparing of motor strength. This clinical trend is not readily explained by the electrophysiologic observations of action potential blockade in large and small fibers perfused to steady state.[6] The mechanisms underlying this divergence between clinical experience and experimental data are poorly understood, but they may be related to the anatomic and geographic arrangement of nerve fibers, variability in the longitudinal spread required for neural blockade, effects on other ion channels, and inherent impulse activity.

SPREAD OF LOCAL ANESTHESIA AFTER INJECTION

When local anesthetics are deposited around a peripheral nerve, they must cross a series of diffusion barriers to access sodium channels in nerve axons (Fig. 10.6). With large nerve trunks, they diffuse from the outer surface (mantle) toward the center (core) of the nerve along a concentration gradient (Fig. 10.7).[7] As a result, nerve fibers located in the mantle of the mixed nerve are blocked first. These mantle fibers are generally distributed to more proximal anatomic structures, whereas distal structures are innervated by fibers near the core. This anatomic arrangement accounts for the initial development of proximal anesthesia with subsequent distal involvement as local anesthetic diffuses to reach more central core nerve fibers. Skeletal muscle weakness may precede sensory blockade if the motor nerve fibers are more superficial. The sequence of onset and recovery from conduction blockade of sympathetic, sensory, and motor nerve fibers in a mixed peripheral nerve depends as much or more on the anatomic location of the nerve fibers within the mixed nerve as on their intrinsic sensitivity to local anesthetics.

PHARMACOKINETICS

For most oral and intravenous drugs, systemic uptake carries the drug from administration site to effect site. Local anesthetics are different: when drug is deposited near the target site, systemic absorption competes with drug entry into effect sites in nerves. Thus, rapid and efficient systemic uptake from an injection site diminishes, rather than increases, efficacy in nerve blockade. This principle is illustrated in Fig. 10.8. High plasma concentrations of local anesthetics after absorption from injection sites (or unintended intravascular injection) are undesirable and are the origin of their potential toxicity. Peak plasma concentrations achieved are determined by the rate of systemic uptake and, to a lesser extent, the rate of clearance of the local anesthetic. Uptake is affected by several factors related to the physiochemical properties of the local anesthetic and local tissue blood flow. Uptake tends to be delayed for local anesthetics with high lipophilicity and protein binding.

Local Anesthetic Vasoactivity

Anesthetics differ in their tendencies to cause either vasoconstriction or vasodilation of blood vessels. These effects vary with site of injection, concentration, and balance of local direct actions on vascular smooth muscle versus indirect actions via blockade of sympathetic efferent fibers. Such differences may be clinically important. For example, the less frequent incidence of systemic toxicity of S (–) ropivacaine compared with the R (+) enantiomer in part may result from its vasoconstrictive activity (see "Adverse Effects"). The variable effect of vasoconstrictors added to local anesthetic solutions used for spinal anesthesia is another example. In contrast to lidocaine or

Table 10.2 Comparative Pharmacology and Common Current Use of Local Anesthetics

Classification and Compounds	pK_a	% Nonionized at pH 7.4	Potency[a]	Max. Dose (mg) for Infiltration[b]	Duration After Infiltration (min)	Topical	Local	IV	Periph	Epi	Spinal
Esters											
Procaine	8.9	3	1	500	45-60	No	Yes	No	Yes	No	Yes
Chloroprocaine	8.7	5	2	600	30-60	No	Yes	Yes	Yes	Yes	Yes[c]
Tetracaine	8.5	7	8	Yes	Yes[d]	No	No	No	Yes		
Amides											
Lidocaine	7.9	24	2	300	60-120	Yes	Yes	Yes	Yes	Yes	Yes[c]
Mepivacaine	7.6	39	2	300	90-180	No	Yes	No	Yes	Yes	Yes[c]
Prilocaine	7.9	24	2	400	60-120	Yes[e]	Yes	Yes	Yes	Yes	Yes[c]
Bupivacaine, levobupivacaine	8.1	17	8	150	240-480	No	Yes	No	Yes	Yes	Yes
Ropivacaine	8.1	17	6	200	240-480	No	Yes	No	Yes	Yes	Yes

[a]Relative potencies vary based on experimental model or route of administration.
[b]Dosage should take into account the site of injection, use of a vasoconstrictor, and patient-related factors.
[c]Use of procaine, lidocaine, mepivacaine, prilocaine, and chloroprocaine for spinal anesthesia is somewhat controversial; indications are evolving (see text).
[d]Used in combination with another local anesthetic to increase duration.
[e]Formulated with lidocaine as eutectic mixture.
Epi, Epidural; *IV*, intravenous; *Periph*, peripheral.

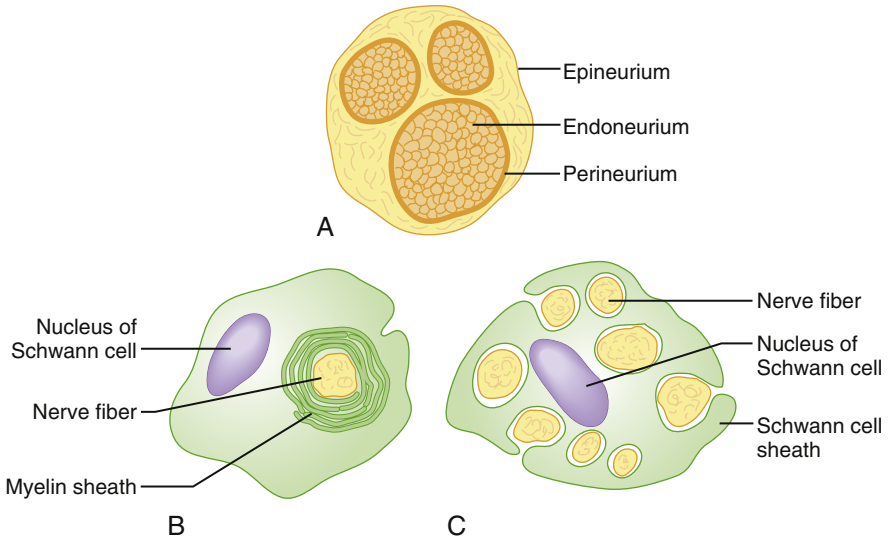

Fig. 10.6 Transverse sections of a peripheral nerve (A) showing the outermost epineurium; the inner perineurium, which collects nerve axons in fascicles; and the endoneurium, which surrounds each myelinated fiber. Each myelinated axon (B) is encased in the multiple membranous wrappings of myelin formed by one Schwann cell, each of which stretches longitudinally more than approximately 100 times the diameter of the axon. The narrow span of axon between these myelinated segments, the node of Ranvier, contains the ion channels that support action potentials. Nonmyelinated fibers (C) are enclosed in bundles of 5 to 10 axons by a chain of Schwann cells that tightly embrace each axon with but one layer of membrane. (From Berde CB, Strichartz GR: Local anesthetics. In Miller RD, Cohen NH, Eriksson LI, et al, eds. *Miller's Anesthesia.* 8th ed. Philadelphia: Saunders Elsevier; 2015.)

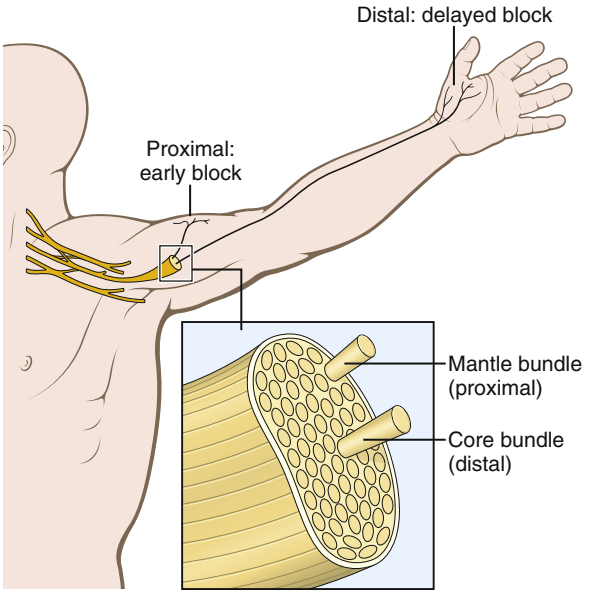

Fig. 10.7 Local anesthetics deposited around a peripheral nerve diffuse along a concentration gradient to block nerve fibers on the outer surface (mantle) before more centrally located (core) fibers. This accounts for early manifestations of anesthesia in more proximal areas of the extremity.

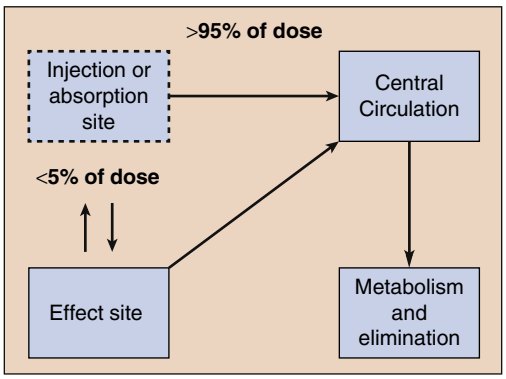

Fig. 10.8 Heuristic model of local anesthetic uptake and distribution. Systemic uptake of local anesthetics from the perineural injection compartment competes with drug entry into nerves. Vasoconstrictors delay systemic uptake from the perineural injection compartment, reducing peak blood concentrations of local anesthetics, and maintaining a higher concentration gradient favoring drug entry into nerves over the first 30 minutes after injection.

bupivacaine, there is some evidence that tetracaine produces a significant increase in spinal cord blood flow. Consequently, prolongation of spinal anesthesia by epinephrine or other vasoconstrictors is more pronounced

with tetracaine than with other commonly used spinal anesthetics.

Metabolism

The amino-ester local anesthetics undergo hydrolysis by plasma esterases, whereas the amino-amide local anesthetics undergo metabolism by hepatic microsomal enzymes. The lungs are also capable of extracting local anesthetics such as lidocaine, bupivacaine, and prilocaine from the circulation. The rate of this metabolism and first-pass pulmonary extraction may influence toxicity (see "Systemic Toxicity"). In this regard, the relatively rapid hydrolysis of the ester local anesthetic chloroprocaine makes it less likely to produce sustained plasma concentrations than other local anesthetics, particularly the amino amides. However, patients with atypical plasma cholinesterase levels may be at increased risk of developing excessive plasma concentrations of chloroprocaine or other ester local anesthetics owing to absent or limited plasma hydrolysis. Hepatic metabolism of lidocaine is extensive, and clearance of this local anesthetic from plasma parallels hepatic blood flow. Liver disease or decreases in hepatic blood flow, as occur with congestive heart failure or general anesthesia, can decrease the rate of metabolism of lidocaine. Less than 5% of injected local anesthetics are excreted unchanged in the urine.

Additives

Epinephrine is the most common additive in local anesthetic solutions. In a typical concentration of 5 μg/mL (1:200,000), epinephrine produces local vasoconstriction, which slows the rate of tissue absorption and therefore reduces peak systemic concentrations, decreasing the odds of systemic toxicity (see later discussion). Depending on injection site and the local anesthetic to which epinephrine is added, epinephrine may result in some prolongation of sensory or motor block. Epinephrine can also be used as a marker for detection of intravascular injection, based on effects on heart rate, arterial blood pressure, or symptoms. However, systemic absorption of epinephrine may contribute to cardiac dysrhythmias or accentuate systemic hypertension in vulnerable patients. Epinephrine should be avoided when performing peripheral nerve blocks in areas that may lack collateral flow (e.g., digital blocks). In contrast, epinephrine-induced vasoconstriction decreases local bleeding and may provide added benefit when combined with local anesthetics used for infiltration anesthesia.

Several other additives have been studied in efforts to prolong analgesia from peripheral nerve blocks, including the α_2-agonist clonidine and the glucocorticoid dexamethasone. Both of these additives cause meaningful prolongations from some blocks more than others, as well as meaningful prolongation of sensory block and clinical analgesia from systemic as well as local perineural administration.[8]

Traditionally, anesthesia providers have exercised considerable freedom in mixing their own additives and combinations. There is a growing recognition that this practice sometimes produces drug administration errors. In addition, although some additives have undergone proper preclinical testing to ensure absence of local tissue toxicities on nerve and muscle, others have not (see "Local Tissue Toxicity"). New additives that lack sufficient preclinical safety data and a regulatory evaluation process probably should not be used clinically.

ADVERSE EFFECTS

Important adverse effects of local anesthetics, although rare, may occur from systemic absorption, local tissue toxicity, allergic reactions, and drug-specific effects.

Systemic Toxicity

Systemic toxicity of local anesthetics results from excessive plasma concentrations of these drugs, most often from accidental intravascular injection during performance of peripheral nerve blocks. Less often, excessive plasma concentrations result from absorption of local anesthetics from tissue injection sites. The magnitude of local anesthetic systemic absorption depends on the dose injected, the specific site of injection, and the inclusion of a vasoconstrictor in the local anesthetic solution. Systemic absorption of local anesthetic is maximal after injection for intercostal nerve blocks and caudal anesthesia, intermediate after epidural anesthesia, and least after brachial plexus blocks (Fig. 10.9).[9]

Clinically significant systemic toxicity results from effects on the central nervous system and cardiovascular system. Establishment of maximal acceptable local anesthetic doses for performance of regional anesthesia is an attempt to limit plasma concentrations that can result from systemic absorption of these drugs (see Table 10.2). However, standard dosage recommendations are not entirely evidence-based and are inconsistent, and they fail to take into account the specific injection-site and patient-related factors.[10] Nonetheless, dosage recommendations represent a starting point for dose adjustments based on clinical circumstances and evolving evidence.

Central Nervous System Toxicity

Increasing plasma concentrations of local anesthetics classically produce circumoral numbness, facial tingling, restlessness, vertigo, tinnitus, and slurred speech, culminating in tonic-clonic seizures, though marked variation from this pattern is quite common.[11] Local anesthetics are neuronal depressants, and onset of seizures likely reflect selective

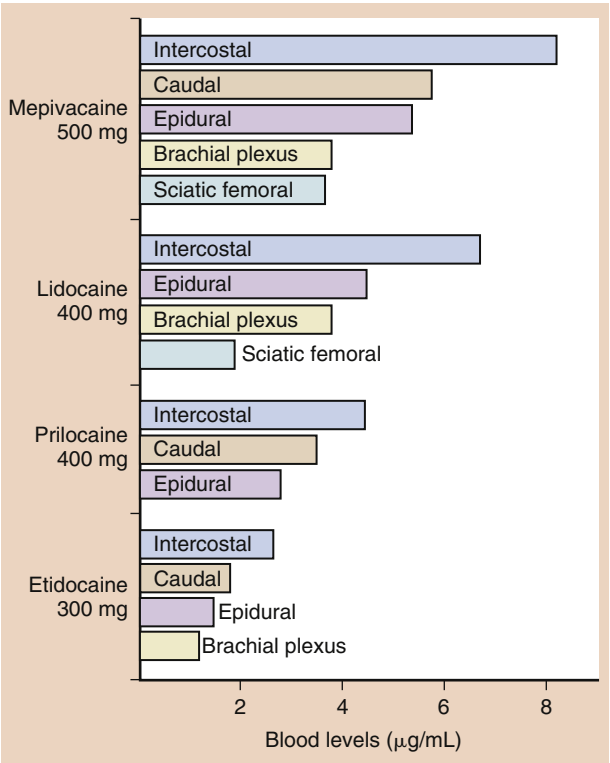

Fig. 10.9 Peak plasma concentrations of local anesthetics resulting during performance of various types of regional anesthetic procedures. (From Covino BD, Vassals HG. *Local Anesthetics: Mechanism of Action in Clinical Use.* Orlando, FL: Grune & Stratton; 1976:97, used with permission.)

depression of cortical inhibitory neurons, leaving excitatory pathways unopposed. However, larger doses may affect inhibitory and excitatory pathways, resulting in central nervous system depression and even coma. These effects generally parallel anesthetic potency. Arterial hypoxemia and metabolic acidosis can occur rapidly during seizure activity, and hypoxemia and acidosis both can enhance the central nervous system toxicity of the local anesthetics.

Treatment of central nervous system toxic reactions begins with prompt intervention with administration of supplemental oxygen and assisting ventilation as indicated to prevent hypoxemia and hypercarbia. Benzodiazepines (i.e., midazolam, lorazepam, diazepam) are generally the drugs of first choice to terminate seizures because of their efficacy and relative hemodynamic stability. Propofol, although more immediately accessible, should be used with caution for seizure suppression as it can compromise cardiac function.

Cardiovascular System Toxicity

The cardiovascular system is generally more resistant to the toxic effects of local anesthetics than the central nervous system. Nevertheless, high plasma concentrations of local anesthetics can produce profound hypotension due to relaxation of arteriolar vascular smooth muscle and direct myocardial depression. The cardiac toxicity, in part, reflects the ability of local anesthetics to block cardiac sodium ion channels as well as other ion channels. As a result, cardiac automaticity and conduction of cardiac impulses are impaired, manifesting on the electrocardiogram as prolongation of the PR interval and widening of the QRS complex. Local anesthetics may profoundly depress myocardial contractility to varying degrees. For example, the ratio of the dose required to produce cardiovascular collapse compared with that producing seizures for lidocaine is about twice that for bupivacaine.[12] Such findings support the concept that bupivacaine is more likely to cause cardiac toxicity, which has been the driving force for development of single-enantiomer anesthetics, such as ropivacaine and levobupivacaine.

Lipid Resuscitation[13-15]

Intravenous infusions of lipid emulsions have become a standard treatment of local anesthetic systemic toxicity (LAST) (also see Chapter 18). The mechanism by which lipid is effective is not clear but is likely related to its ability to extract bupivacaine (or other lipophilic drugs) from aqueous plasma or tissue targets, thus reducing their effective free concentration ("lipid sink"). Accordingly, solutions of lipid emulsion should be stocked and readily accessible in any area where major conduction blockade is performed, as well as locations where overdoses from any lipophilic drug might be treated. A more detailed discussion of this topic and guidelines for administration of lipid emulsions (20%), checklists, and treatment protocols can be found in a publication by the American Society of Regional Anesthesia and Pain Medicine (ASRA) Task Force on Local Anesthetic Systemic Toxicity.[10,16,17]

According to the ASRA guidelines, an intravenous bolus dose of lipid emulsion starts with a bolus of 1.5 mL/kg (100 mg in adults) followed by a continuous infusion at 0.25 mL/kg/min. Although lipid rescue is important and should be used, it is not 100% effective and not a substitute for following dosing guidelines and safe practice regarding patient monitoring, fractionated dosing, and observation for early warning signs of systemic toxicity.

ASRA guidelines recommend additional modifications of standard advanced cardiac life support (ACLS) protocols, including avoidance of vasopressin, calcium channel blockers, β-adrenergic blockers, or other local anesthetics (lidocaine, amiodarone). Incremental dosing of epinephrine should be decreased to less than 1 μg/kg.[10]

Local Tissue Toxicity

Local anesthetics are in general well tolerated in terms of their local tissue effects. Nevertheless, all currently available local

anesthetics have intrinsic toxicities to nerve and muscle that occasionally become clinically apparent. These incidences of toxicities increase with local tissue concentration[18] and duration of exposure, and these risks may be exacerbated by factors that increase nerve vulnerability and predispose to nerve ischemia, including preexisting nerve dysfunction, metabolic and inflammatory conditions, increased tissue pressure, and systemic hypotension. Intraneural concentrations can rise steadily during prolonged perineural infusions. For these reasons, for prolonged perineural infusions, we recommend use of relatively dilute local anesthetic concentrations, generally no more than 0.2% for bupivacaine or ropivacaine.

Allergic Reactions

Allergic reactions to local anesthetics are rare, despite the frequent use of these drugs. Less than 1% of all adverse reactions to local anesthetics are caused by allergic mechanisms. Most adverse responses attributed to allergic reactions are instead due to additives or manifestations of systemic toxicity from excessive plasma concentrations of the local anesthetic. Hypotension associated with syncope may be vagally mediated, whereas tachycardia and palpitations may occur from systemic absorption of epinephrine.

Cross-Sensitivity

The amino-ester local anesthetics, which produce metabolites related to para-aminobenzoic acid, are more likely to evoke hypersensitivity reactions than the amino amides. Allergic reactions may also be caused by methylparaben or similar compounds that resemble para-aminobenzoic acid, which are used as preservatives in commercial formulations of ester and amide local anesthetics. Although patients known to be allergic to amino-ester local anesthetics can receive amino-amide local anesthetics, this recommendation should be cautiously accepted because it assumes that the local anesthetic was responsible for evoking the initial allergic reaction, rather than a common preservative.

Documentation

Documentation of an allergy to local anesthetics is based principally on clinical history (e.g., rash, laryngeal edema, hypotension, bronchospasm). However, increases of serum tryptase, a marker of mast cell degranulation, may have some value with respect to confirmation, and intradermal testing may help establish the local anesthetic as the offending antigen if other drugs (e.g., sedative-hypnotics, opioids) have been administered concurrently.

SPECIFIC LOCAL ANESTHETICS

Amino Esters

Procaine

The earliest injectable local anesthetic, procaine, enjoyed extensive use during the first half of the past century, primarily as a spinal anesthetic. Its instability and the considerable potential for hypersensitivity reactions resulted in limited use after the introduction of lidocaine. Concerns regarding transient neurologic symptoms (TNS) associated with spinal lidocaine (see "Lidocaine") have renewed interest in procaine as a spinal anesthetic. However, limited data suggest that procaine offers only a small advantage with respect to TNS, and spinal procaine is associated with a significantly greater incidence of nausea.[19]

Tetracaine

Tetracaine is still commonly used for spinal anesthesia. As such, it has a long duration of action, particularly if used with a vasoconstrictor, although this combination results in a surprisingly high risk of TNS.[20] Tetracaine is available as a 1% solution or as Niphanoid crystals; the crystal form is preferable because of the relative instability of the anesthetic in solution. Tetracaine is rarely used for epidural anesthesia or peripheral nerve blocks because of its slow onset, profound motor blockade, and potential toxicity when administered at high doses. Although it is an ester, its rate of metabolism is one fourth that of procaine and one tenth that of chloroprocaine.

Chloroprocaine

Chloroprocaine initially gained popularity as an epidural anesthetic, particularly in obstetrics, because its rapid hydrolysis virtually eliminated concern about systemic toxicity and fetal exposure to the local anesthetic. Unfortunately, neurotoxic injury, presumed to occur from accidental intrathecal injection of large doses intended for the epidural space, tempered enthusiasm for neuraxial administration of chloroprocaine. This toxicity was thought to be caused by the preservative, sodium bisulfite, contained in the commercial formulation.[21] However, subsequent studies do not demonstrate neurotoxicity from intrathecal bisulfite; instead it was found not to be neurotoxic and may even have neuroprotective effects.[22] In any event, a formulation of chloroprocaine devoid of preservatives and antioxidants is available.

Chloroprocaine produces epidural anesthesia of a relatively short duration. Epidural administration of chloroprocaine is sometimes avoided because it impairs the anesthetic or analgesic action of epidural bupivacaine and of opioids used concurrently or sequentially.[23] Chloroprocaine has been reevaluated as a spinal anesthetic,[24-26] reflecting clinical concerns related to the possible toxicity of lidocaine placed in the subarachnoid space,[27] and the small doses required for spinal anesthesia would not be predicted to produce toxicity. These initial reports have been encouraging, and the off-label use of chloroprocaine for this purpose is now common. Despite the controversy, chloroprocaine solutions used for spinal

anesthesia should be bisulfite-free, and the intrathecal dose should not exceed 60 mg.

Because of its rapid plasma clearance, chloroprocaine has two unique roles in pediatric regional anesthesia: (1) as a continuous epidural infusion in neonates and very young infants, and (2) for repeat loading doses in patients receiving postoperative epidural or peripheral perineural infusions, in the setting where a repeat loading dose with the more commonly used amino-amide local anesthetics would result in stepwise increase of blood concentrations into a toxic range.

Amino Amides

Lidocaine

Lidocaine is the most commonly used local anesthetic. It is used for local, topical, and regional intravenous block, peripheral nerve block, and spinal and epidural anesthesia. Although recent issues have led to restricted use of lidocaine for spinal anesthesia, this local anesthetic remains popular for all other applications, including epidural anesthesia.

Potential neurotoxicity (i.e., cauda equina syndrome) when lidocaine is administered for spinal anesthesia has emerged as a concern, especially when used with a continuous spinal technique.[28] Most of the initial injuries resulted from neurotoxic concentrations of anesthetic in the caudal region of the subarachnoid space achieved by the combination of maldistribution and relatively large doses of anesthetic administered through small-gauge spinal catheters.[29] However, even doses of lidocaine routinely used for single-injection spinal anesthesia (75 to 100 mg) have been associated with neurotoxicity.[27]

TNS is a syndrome of pain and dysesthesia that may occur in up to one third of patients receiving intrathecal doses of lidocaine (but rarely occurs with bupivacaine).[20,30,31] These symptoms were initially called transient radicular irritation, but this term was later abandoned in favor of TNS because of the lack of certainty regarding their cause. In addition to the use of intrathecal lidocaine, cofactors that contribute to the occurrence of TNS include the lithotomy position,[20,30] positioning for knee arthroscopy,[30] and outpatient status.[20] In contrast, local anesthetic concentration, the presence of glucose, concomitant administration of epinephrine, and technique-related factors such as the size or type of needle do not alter the incidence of TNS with lidocaine.[20]

Symptoms of TNS generally manifest within the first 12 to 24 hours after surgery, most often resolve within 3 days, and rarely persist beyond a week. Although self-limited, the pain can be quite severe, often exceeding that induced by the surgical procedure, and on rare occasions requiring rehospitalization for pain control. Nonsteroidal antiinflammatory drugs are often fairly effective and should be used as first-line treatment. TNS is not associated with sensory loss, motor weakness, or bowel and bladder dysfunction. The cause and significance of these symptoms remain to be established, but discrepancies between factors affecting TNS and experimental animal toxicity cast doubt that TNS and persistent neurologic deficits (e.g., cauda equina syndrome) are mediated by the same mechanism.

Mepivacaine

Mepivacaine was the first in the series of pipecholyl xylidines, combining the piperidine ring of cocaine with the xylidine ring of lidocaine (see Fig. 10.2). This resulted in an anesthetic with characteristics very similar to lidocaine, although with less vasodilation, and a slightly longer duration of action. The clinical use of mepivacaine parallels lidocaine, with the exception that it is relatively ineffective as a topical local anesthetic. Mepivacaine's lower incidence of TNS makes it an attractive alternative to lidocaine for short-duration spinal anesthesia.

Prilocaine

Prilocaine was introduced into clinical practice with the anticipation that its rapid metabolism and infrequent acute toxicity (central nervous system toxicity about 40% less than lidocaine) would make it a useful drug. Unfortunately, administration of large doses (>600 mg) may result in clinically significant accumulation of the metabolite ortho-toluidine, an oxidizing compound capable of converting hemoglobin to methemoglobin. Prilocaine-induced methemoglobinemia spontaneously subsides and can be reversed by the administration of methylene blue (1 to 2 mg/kg given intravenously over a 5-minute period). Nevertheless, the capacity to induce dose-related methemoglobinemia has limited the clinical acceptance of prilocaine.

Similar to other anesthetics, prilocaine has recently received attention as a spinal anesthetic, owing to dissatisfaction with spinal lidocaine. Available data, albeit limited, suggest prilocaine has a duration of action similar to lidocaine with a lower incidence of TNS. Prilocaine is not currently approved for use in the United States, nor is there any formulation available that would be appropriate for intrathecal administration.

Bupivacaine

Bupivacaine is a congener of mepivacaine, with a butyl rather than a methyl group on the piperidine ring, a modification that imparts a longer duration of action. This characteristic, combined with its high-quality sensory anesthesia relative to motor blockade, has established bupivacaine as the most commonly used local anesthetic for epidural anesthesia during labor and for postoperative pain management. Bupivacaine is also commonly used

for peripheral nerve block, and it has a relatively unblemished record as a spinal anesthetic.

Refractory cardiac arrest has been associated with the use of 0.75% bupivacaine when accidentally injected intravenously during attempted epidural anesthesia,[32] and this concentration is no longer recommended for epidural anesthesia. The most likely mechanism for bupivacaine's cardiotoxicity relates to the nature of its interaction with cardiac sodium ion channels.[33] When electrophysiologic differences between anesthetics are compared, lidocaine enters the sodium ion channel quickly and leaves quickly. In contrast, recovery from bupivacaine blockade during diastole is relatively prolonged, making it far more potent with respect to depressing the maximum upstroke velocity of the cardiac action potential (V_{max}) in ventricular cardiac muscle. As a result, bupivacaine has been labeled a "fast-in, slow-out" local anesthetic. This characteristic likely creates conditions favorable for unidirectional block and reentry. Other mechanisms may contribute to bupivacaine's cardiotoxicity, including disruption of atrioventricular nodal conduction, depression of myocardial contractility, and indirect effects mediated by the central nervous system.[34] This potential for cardiotoxicity places important limitations on the total dose of bupivacaine, and it underscores the vital role of fractional dosing and methods to detect inadvertent intravascular injection when large doses of local anesthetic (especially bupivacaine) are given for regional block. The recent identification of lipid emulsion as a therapeutic intervention for bupivacaine cardiotoxicity does not diminish the critical importance of these preventive measures. Cardiotoxicity is of no concern when small doses are administered for spinal anesthesia.

Single Enantiomers

Concerns for bupivacaine cardiotoxicity have focused attention on the stereoisomers of bupivacaine and on its homolog, ropivacaine.

Stereochemistry

Isomers are different compounds that have the same molecular formula. Subsets of isomers that have atoms connected by the same sequence of bonds but that have different spatial orientations are called stereoisomers. Enantiomers are a particular class of stereoisomers that exist as mirror images. The term *chiral* is derived from the Greek *cheir,* meaning "hand," because the forms can be considered nonsuperimposable mirror images. Enantiomers have identical physical properties except for the direction of the rotation of the plane of polarized light. This property is used to classify the enantiomer as dextrorotatory (+) if the rotation is to the right or clockwise and as levorotatory (–) if it is to the left or counterclockwise. A racemic mixture is a mixture of equal parts of enantiomers and is optically inactive because the rotation caused by the molecules of one isomer is canceled by the opposite rotation of its enantiomer. Chiral compounds can also be classified on the basis of absolute configuration, generally designated as R (rectus) or S (sinister). Enantiomers may differ with respect to specific biologic activity. For example, the S (–) enantiomer of bupivacaine has inherently less cardiotoxicity than its R (+) mirror image.

Ropivacaine

Ropivacaine (levopropivacaine) is the S (–) enantiomer of the homolog of mepivacaine and bupivacaine with a propyl tail on the piperidine ring. In addition to a more favorable interaction with cardiac sodium ion channels. It has a more likely propensity to produce vasoconstriction, which may contribute to its reduced cardiotoxicity.

Motor blockade is less pronounced, and electrophysiologic studies raise the possibility that C fibers are preferentially blocked, together suggesting that ropivacaine may more easily produce a differential block. However, as expected from its lower lipid solubility, ropivacaine is less potent than bupivacaine. The question of potency is critical to any comparison of these anesthetics; if more drug needs to be administered to achieve a desired effect, the apparent benefits with respect to cardiotoxicity (or differential block) may not exist when more appropriate equipotent dose comparisons are made. Ropivacaine likely offers some advantage with respect to cardiotoxicity, but any benefit over bupivacaine with respect to differential block is marginal, at best.

Levobupivacaine

Levobupivacaine is the single S (–) enantiomer of bupivacaine. Similar to ropivacaine, cardiotoxicity is reduced, but there is no advantage over bupivacaine with respect to differential blockade. As with ropivacaine, the clinically significant advantage of this compound over the racemic mixture is restricted to situations in which relatively high doses of anesthetic are administered.

Topical Local Anesthetics

Local anesthetics are commonly administered on mucosal surfaces,[35] on cut skin to facilitate laceration repair,[36] and on intact skin, especially for needle procedures in children. Systemic absorption through mucosal surfaces is relatively rapid and efficient. Systemic toxicity is a recognized problem with excessive dosing of local anesthetic sprays and gels from the oral, nasal, or tracheobronchial mucosa, particularly in infants and children.

The keratinized layer of the skin provides an effective barrier to diffusion of topical anesthetics, making

it relatively more difficult to achieve anesthesia of intact skin by topical application. This limitation can be overcome by using relatively high concentrations of local anesthetic (e.g., 5% lidocaine as in LMX or tetracaine 4% gel as in Ametop). A combination of 2.5% lidocaine and 2.5% prilocaine cream (i.e., eutectic mixture of local anesthetics [EMLA]) is widely used on intact skin.[37,38] This mixture has a lower melting point than either component, and it exists as an oil at room temperature that is capable of overcoming the barrier of the skin. EMLA cream is particularly useful in children (also see Chapter 34) for the prevention or attentuation of pain associated with venipuncture or placement of an intravenous catheter, although it may take up to an hour before adequate topical anesthesia is produced. Another product, Synera, uses a heating element to accelerate onset of skin analgesia from a lidocaine-tetracaine patch.

Tumescent Local Anesthesia

A variety of plastic and cosmetic surgical procedures are commonly performed by a technique known as tumescent local anesthesia, which involves subcutaneous infusion of large volumes of very dilute local anesthetic.[39-41] The total lidocaine doses used in this approach are very large, such as eightfold larger than recommended doses for infiltration or peripheral nerve blockade. Nevertheless, there is a pharmacokinetic basis for this approach. When recommended dose guidelines and techniques are followed, plasma lidocaine concentrations remain in a safe range, though plasma concentrations commonly peak more than 12 hours after injection. Several case series support the general safety of this approach when recommended guidelines are followed. Conversely, adverse events have occurred when guidelines were not followed. In particular, additional dosing of other local anesthetics over the next day has resulted in toxic reactions. Any health facility using this technique should have resources and protocols for treatment of LAST.

Systemic Local Anesthetics for Acute and Chronic Pain

Local anesthetics and related sodium channel blockers such as mexiletine can be administered as systemic analgesics as well as for local anesthesia. There is evidence for effectiveness as adjuvant analgesics for postoperative pain[42] as well as for several types of neuropathic pain.[43] For some patients with neuropathic pain, brief intravenous lidocaine infusions may produce a remarkable, though poorly understood, extended duration of pain relief (e.g., for days or weeks) that far outlasts any apparent pharmacologic duration of lidocaine.[18,44]

WHEN LOCAL ANESTHESIA FAILS

Anesthesia providers and all clinicians should strive to improve the reliability of clinical use of local anesthetics. Historically, a common cause of failed local anesthesia has been technical failure; that is, needle placement and injection of the solution not sufficiently close to the intended site of action. The widespread use of ultrasound guidance has clearly improved technical success of many forms of regional anesthesia, especially involving peripheral nerve and plexus blocks (also see Chapter 18). Although multiple studies indicate that ultrasound facilitates more successful rates of regional anesthesia with much smaller volumes of local anesthetics, the median effective dose or volume (i.e., effectiveness for 50% of subjects) is not a relevant variable for clinical practice; what is more relevant is an ED_{95} (an effective dose preventing movement in 95% of subjects).[45] Long-established techniques, such as thoracic epidural anesthesia, have significant technical failure rates when inserted using solely "blind" techniques such as loss of resistance. There is a growing appreciation for more extensive roles for more objective approaches for confirmation of needle and catheter placement for many forms of regional anesthesia in addition to ultrasound, such as Tsui's nerve stimulation approach for epidural catheter placement,[46] transduction of epidural space pressure waves, and selective use of fluoroscopy[47] (also see Chapters 17 and 18).

Aside from technical failure in needle location, local anesthesia can fail for a range of other reasons. Clinicians can make erroneous assumptions about the relevant neuroanatomy of pain arising from a surgical procedure, leading to coverage of an inadequate subset of the nerves innervating a surgical site.

In addition, there is an underappreciation of biologic sources of variation in local anesthetic responsiveness. For example, some patients with Ehlers-Danlos syndrome type III show relative resistance to local anesthetics.[48]

Local anesthetics commonly have diminished effectiveness in sites of infection or inflammation. Inflammation-induced local anesthetic resistance probably results from both pharmacokinetic factors (local acidosis, edema, hyperemia) that reduce drug entry into nerves, as well as pharmacodynamic factors, including peripheral and central sensitization.[49]

Rapidly developing tolerance (tachyphylaxis) can occur in some patients with repeated dosing or prolonged infusion. Animal studies[50] and clinical observations[51] associate tachyphylaxis with the development of hyperalgesia. Tachyphylaxis can be diminished or prevented by coadministration of antihyperalgesic drugs or other analgesics with central actions.[52]

Patients with long-standing chronic pain and hyperalgesia often appear to require larger volumes or concentrations, or both, of local anesthetics to achieve

adequate analgesia, as well as coadministration of other analgesic or antihyperalgesic drugs. Although psychological factors may influence a patient's ability to tolerate surgery with regional anesthesia, clinicians should avoid "blaming the patient" for insufficient degrees of sensory block or analgesia due to a variety of technical or biologic factors that influence block effectiveness.

There are other possible effects of chronic pain and its treatment on peripheral nerves and sodium channels. Nerve injury and inflammation change the expression of different sodium channel subtypes. Although the alpha subunit of the sodium channel composes the "pore," beta subunits are also differentially expressed following nerve injury or inflammation and these beta subunits modulate channel electrophysiology and thereby may alter local anesthetic responsiveness. A 2016 study reported that chronic, but not acute, opioid exposure caused impaired local anesthetic responsiveness in the rat sciatic nerve.[53]

FUTURE LOCAL ANESTHETICS

Local anesthetics play a central role in modern anesthetic practice. However, despite major advances in pharmacology and techniques for administration over the past century, this class of compounds has a relatively narrow therapeutic index with respect to their potential for neurotoxicity and for adverse cardiovascular and central nervous system effects. Another class of molecules that block sodium channels by a different site and mechanism are called the *site 1 sodium channel blockers*. They appear devoid of neurotoxicity and myotoxicity in some preliminary studies.[54,55] These observations suggest that sodium channel blockade and local tissue toxicity to nerve and muscle may not be mediated by a common mechanism. Site 1 blockers also appear to have minimal cardiotoxicity,[56] probably owing to their much weaker affinity for the predominant sodium channel subtype in the myocardium, Nav1.5.

Regional anesthesia has assumed growing importance in postoperative analgesia as well as intraoperatively (also see Chapters 17, 18, and 40). Opioid sparing per se is recognized as a beneficial consequence of using regional anesthesia and analgesia. Available local anesthetics typically provide less than 12 hours of analgesia following a single injection. Although analgesia can be prolonged using continuous catheter approaches, these infusions involve additional potential for dislodgement, additional postoperative care and expense, and some risks. Therefore, there have been several approaches to producing prolonged local anesthesia for wound infiltration or peripheral nerve blockade via a single injection. Controlled release of bupivacaine has been achieved from microparticles, liposomes, hydrogels, and other vehicles. One liposomal bupivacaine product, Exparel, is now on the market in the United States with approval for wound infiltration. In clinical trials, outcomes have been mixed.[57,58]

Our group* is actively investigating the site 1 sodium channel blockers in animals[59] and in early clinical trials.[60] Site 1 blockers show profound synergism with existing local anesthetics and marked prolongation by epinephrine.

Another limitation of existing local anesthetics is the absence of modality selectivity. For example, in epidural analgesia for labor, it would be very desirable to have intense analgesia, avoidance of weakness and hypotension, and preservation of sufficient sensation to feel an urge to push (also see Chapter 33). Recent research has approached sensory-selective blockade by two predominant strategies: (1) targeting local anesthetic entry preferentially into small sensory nerve fibers[61] and (2) developing drugs that bind preferentially to subtypes of sodium channels located predominantly in small sensory fibers.

CONCLUSIONS

Local anesthetics are used widely in anesthesiology and many areas of medicine. They have some risks and side effects, but they can be used with very good safety and clinical effectiveness by attention to safe dosing guidelines, early recognition of intravascular injection, and optimal technique. Local anesthetics are not a "solved problem," and current research may lead to improvements in regional anesthesia and postoperative care in the future.

QUESTIONS OF THE DAY

1. What is the site of action of local anesthetics? How do local anesthetics block impulse conduction from an electrophysiologic perspective?
2. What is the typical pattern of local anesthetic spread after injection near a peripheral nerve? What are the expected clinical manifestations of this pattern of spread?
3. What are the potential advantages to the use of epinephrine as a local anesthetic additive? In what situations should epinephrine be avoided as an additive?

*Disclosure—Charles B. Berde, his collaborators, and Boston Children's Hospital have licensed the site 1 blocker neosaxitoxin for commercial development, with a potential for future milestone payments and royalties.

4. What are the central nervous system and cardiovascular manifestations of local anesthetic toxicity?
5. What is the initial dose of intravenous lipid emulsion for treatment of local anesthetic systemic toxicity (LAST)? What are the recommended modifications to advanced cardiac life support in a patient with LAST?
6. Besides technical failure in local anesthesia injection, what factors can explain the inability to achieve satisfactory local anesthetic block for a given patient?

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