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 a narrow class of compounds, and recovery is normally spontaneous, predictable, and complete.

Cocaine’s systemic toxicity, its irritant properties when placed topically or around nerves, and its substantial potential for physical and psychological dependence generated interest in identification of an alternative local anesthetic. Because cocaine was known to be a benzoic acid ester (Fig. 11-1), developmental strategies focused on this class of chemical compounds. Although benzoic acid was identified before the turn of the century, its poor water solubility restricted its use to topical anesthesia, for which it still finds some limited application in modern clinical practice. The first useful injectable local anesthetic, procaine, can be considered the prototype on which all commonly used local anesthetics are based. The procaine molecule is derived from an aromatic acid (para-aminobenzoic acid) and an amino alcohol, yielding a structure with three distinct regions: an aromatic head, which imparts lipophilicity; a terminal amine tail, a proton acceptor that imparts hydrophobicity; and a hydrocarbon chain attached to the aromatic acid by an ester linkage (Fig. 11-2). Several other derivatives of para-aminobenzoic acid were developed as local anesthetics during the first half of the past century, most notably tetracaine and chloroprocaine, both embodying modifications of the aromatic ring (Fig. 11-3).

In 1948, lidocaine was introduced, and it was the first departure from the amino-ester series. Being derived from an aromatic amine (i.e., xylidine) and an amino acid, the hydrocarbon chain and the aromatic head of
the lidocaine molecule are linked by an amide bond (rather than an ester), imparting greater stability. This molecular structure also averts the allergic reactions commonly associated with ester anesthetics (which result from sensitivity to the cleaved aromatic acid). Because of these favorable properties, lidocaine became the template for the development of a series of amino-amide anesthetics (see Fig. 11-3). Most amino-amide local anesthetics are derived from xylidine, including mepivacaine, bupivacaine, ropivacaine, and levobupivacaine (see Fig. 11-1). In contrast to lidocaine, the terminal amino portion of these newer compounds is contained within a piperidine ring (see Fig. 11-1), and the series is commonly referred to as pipercholyl xylidines. 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”). Because they are amides, all of the newer local anesthetics require biotransformation in the liver rather than undergoing ester hydrolysis in plasma, as is the case for the amino-esters.

**MECHANISMS OF ACTION AND FACTORS AFFECTING BLOCK**

**Nerve Conduction**

Local anesthetics block the transmission of the action potential by inhibition of voltage-gated sodium ion channels. 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 active outward transport of sodium and inward transport of potassium ions, combined with a membrane that is relatively permeable to potassium and relatively impermeable 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 depolarization, after which the resting membrane potential is reestablished. From an electrophysiologic standpoint, local anesthetics block conduction of neural transmission 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.

**Anesthetic Effect and the Active Form of the Local Anesthetic**

Local anesthetics exert their electrophysiologic effects by blocking sodium ion conductance. This effect is primarily mediated by interaction with specific receptors that are within the inner vestibule of the sodium ion channel. The commonly used injectable local anesthetics exist in two forms that are in dynamic equilibrium, an uncharged base or a protonated quaternary amine. Most likely, the charged form of the local anesthetic molecule binds to the receptor and is responsible for the predominant action of these drugs. However, the pharmacology is a bit more complex, as the charged structure is highly hydrophilic, and relatively incapable of penetrating the nerve membrane to reach its site of action. The neutral base plays a critical role in the local anesthetic effect by permitting the anesthetic to penetrate the nerve membrane to gain access to the receptor (Fig. 11-4). After penetration, re-equilibration occurs, permitting the charged form of the local anesthetic to bind. These drugs also may reach the sodium channel laterally
(i.e., hydrophobic pathway). Yet this mechanism cannot completely account for all of the local anesthetic effect. For example, benzocaine exists only in an uncharged form, and it is not affected by pH, but it still possesses local anesthetic activity.

**Sodium Ion Channel State, Anesthetic Binding, and Use-Dependent Block**

According to the modulated receptor model, sodium ion channels alternate between several conformational states, and local anesthetics bind to these different conformational states with different affinities. During excitation, the sodium channel moves from a resting-closed state to an activated-open state, with passage of sodium ions and consequent depolarization. After depolarization, the channel assumes an inactivated-closed conformational state. Local anesthetics bind to the activated and inactivated states more readily than the resting state, attenuating conformational change. Drug dissociation from the inactivated conformational state is slower than from the resting state. Thus, repeated depolarization produces more effective anesthetic binding. The electrophysiologic consequence of this effect is progressive...
enhancement of conduction blockade with repetitive stimulation, an effect referred to as use-dependent or frequency-dependent block. For this reason, selective conduction blockade of nerve fibers by local anesthetics may in part be related to the characteristic frequency of activity of the nerve.

**Critical Role of pH**

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 ($K_a$) can be expressed as follows:

$$pK_a = pH - \log[base]/[conjugate\ acid]$$

If the concentration of the base and conjugate acid are equal, the latter component of the equation cancels (because $\log 1 = 0$). Thus, the $pK_a$ provides a useful way to describe the propensity of a local anesthetic to exist in a charged or an uncharged state. The lower the $pK_a$, the greater is the percent of un-ionized fraction at a given pH. For example, the highly lipophilic compound benzocaine has a $pK_a$ of 3.5, and the molecule exists solely as the neutral base under physiologic conditions. In contrast, because the $pK_a$ 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 11-1). Because local anesthetics are poorly soluble in water, they are generally marketed as water-soluble hydrochloride salts. These hydrochloride salt solutions are acidic, contributing to the stability of local anesthetics but potentially impairing the onset of a block. Bicarbonate is sometimes added to local anesthetic solutions 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, may likewise have a negative impact on the onset and quality of local anesthesia.

**Lipid Solubility**

Lipid solubility of a local anesthetic affects its tissue penetration and its uptake in the nerve membrane. This physiochemical property impacts the fundamental characteristics of local anesthetics. Lipid solubility is ordinarily expressed as a partition coefficient, which is determined by comparing the solubility of the drug in a nonpolar solvent, such as $n$-heptane or octanol, with the solubility in an aqueous phase, generally water or buffered solution. Although results may vary depending on the specific methodology, lipid solubility generally correlates with local anesthetic potency and duration of action, and to a lesser extent, it varies inversely with latency or the time to onset of local anesthetic effect. Duration of the local anesthetic effect also correlates with protein binding, which likely serves to retain anesthetic within the nerve.

When considering physiochemical characteristics as they relate to the local anesthetic effect, it is important to appreciate that measures of anesthetic activity may also be impacted 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 generally equipotent when assessed in intact in vivo systems. Even within in vivo systems, comparisons among local anesthetics may vary based on the model or 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**

Nerve fibers can be classified according to fiber diameter, presence (type A and B) or absence (type C) of myelin, and function (Table 11-2). 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
<table>
<thead>
<tr>
<th>Classification and Compounds</th>
<th>pKₐ</th>
<th>% Nonionized at pH 7.4</th>
<th>Potency</th>
<th>Max. Dose (mg) for Infiltration</th>
<th>Duration after Infiltration (min)</th>
<th>Topical</th>
<th>Local</th>
<th>IV</th>
<th>Periph</th>
<th>Epi</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esters</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td>8.9</td>
<td>3</td>
<td>1</td>
<td>500</td>
<td>45-60</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>8.7</td>
<td>5</td>
<td>2</td>
<td>600</td>
<td>30-60</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8.5</td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td><strong>Amides</strong></td>
<td></td>
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</tr>
<tr>
<td>Lidocaine</td>
<td>7.9</td>
<td>24</td>
<td>2</td>
<td>300</td>
<td>60-120</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>7.6</td>
<td>39</td>
<td>2</td>
<td>300</td>
<td>90-180</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.9</td>
<td>24</td>
<td>2</td>
<td>400</td>
<td>60-120</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bupivacaine, levobupivacaine</td>
<td>8.1</td>
<td>17</td>
<td>8</td>
<td>150</td>
<td>240-480</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.1</td>
<td>17</td>
<td>6</td>
<td>200</td>
<td>240-480</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Relative potencies vary based on experimental model or route of administration.

1Dosage should take into account the site of injection, use of a vasoconstrictor, and patient-related factors.

Use of procaine, lidocaine, mepivacaine, prilocaine, and chloroprocaine for spinal anesthesia is somewhat controversial; indications are evolving (see text).

Used in combination with another local anesthetic to increase duration.

Formulated with lidocaine as eutectic mixture.

Epi, epidural; IV, intravenous; Periph, peripheral.
interruptions in the myelin sheath (i.e., nodes of Ranvier). With respect to local anesthetic effect, conduction block-ade is predictably absent if at least three successive nodes of Ranvier are exposed to adequate concentrations of local anesthetics. However, the observation that sensitivity to local anesthetic blockade is inversely related to nerve fiber diameter probably does not reflect cause and effect. There is actually evidence to suggest that large, myelinated nerve fibers are more sensitive to local anesthetic blockade than smaller, unmyelinated fibers. Nonetheless, in clinical practice, incremental increases in the concentrations of local anesthetics result in progressive interruption of transmission of autonomic, sensory, and motor neural impulses and therefore production of autonomic nervous system blockade, sensory anesthesia, and skeletal muscle paralysis. 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.

**PROPENSITY TO INDUCE DIFFERENTIAL BLOCKADE**

Local anesthetics are not equivalent in their propensity to induce differential blockade. For example, for equivalent analgesic or local anesthetic effect, etidocaine produces more profound motor block than bupivacaine. This characteristic makes bupivacaine a more valuable drug, particularly for use in labor or for postoperative pain management, and it accounts for etidocaine’s limited use in clinical anesthesia. Attempts to identify local anesthetics with far greater sensory selectivity have been largely unsuccessful, although such effects can be achieved with alternative compounds under certain circumstances, such as that achieved with spinal administration of opioids.

**Spread of Local Anesthesia after Injection**

When local anesthetics are deposited around a peripheral nerve, they diffuse from the outer surface (mantle) toward the center (core) of the nerve along a concentration gradient (Fig. 11-5). 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 anesthe-sia with subsequent distal involvement as local anesthetic diffuses to reach more central core nerve fibers. Consequently, skeletal muscle paralysis may precede the onset of 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.

<table>
<thead>
<tr>
<th>Table 11-2 Classification of Nerve Fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fiber</strong></td>
</tr>
<tr>
<td>A (myelinated)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>B (myelinated)</td>
</tr>
<tr>
<td>C (unmyelinated)</td>
</tr>
</tbody>
</table>

**Figure 11-5** 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.
Local anesthetics differ from most drugs used in medicine because they are deposited at the target site, and systemic absorption and circulation attenuate or curtail the drug’s effect rather than deliver the drug to its intended site of action. 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 somewhat in their vasoactivity, but most are vasodilators at clinically relevant concentrations, although this effect varies with site of injection. Such differences may be clinically important. For example, the lower 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 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, 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 due 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. Low water solubility of local anesthetics usually limits renal excretion of the parent compound to less than 5% of the injected dose.

**Vasoconstrictors**

Addition of a vasoconstrictor (e.g., 1:200,000 or 5 μg/mL of epinephrine) to local anesthetic solutions used for infiltration, peripheral block, and epidural or spinal anesthesia produces local vasoconstriction, which limits systemic absorption of local anesthetic and prolongs the duration of action while having little effect on the onset of anesthesia. Decreased systemic absorption of local anesthetic increases the likelihood that the rate of metabolism will match the rate of absorption, decreasing the possibility of systemic toxicity. Epinephrine may also decrease the likelihood of a systemic reaction by serving as a marker for detection of intravascular injection. 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.

**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 greatest after injection for intercostal nerve blocks and caudal anesthesia, intermediate after epidural anesthesia, and least after brachial plexus blocks (Fig. 11-6). Infiltration anesthesia produces local vasoconstriction, which limits systemic absorption of local anesthetic and prolongs the duration of action while having little effect on the onset of anesthesia. Decreased systemic absorption of local anesthetic increases the likelihood that the rate of metabolism will match the rate of absorption, decreasing the possibility of systemic toxicity. Epinephrine may also decrease the likelihood of a systemic reaction by serving as a marker for detection of intravascular injection. 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.

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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 11-1). However, standard dosage recommendations are not evidence-based, are inconsistent, and they fail to take into account the specific injection site and patient-related factors.\(^6\) Nonetheless, dosage recommendations represent guidelines for providing a starting point from which adjustments based on clinical circumstances and evolving evidence can be made.

**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.\(^7\) Local anesthetics are neuronal depressants, and onset of seizures is thought to reflect selective 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 acidosis potentiates the central nervous system toxicity of the local anesthetics.

Early tracheal intubation to facilitate ventilation and maintenance of oxygenation may be prudent, and is essential in patients at risk for aspiration. Neuromuscular blocking drugs can stop the peripheral manifestations of seizure activity but not the underlying central nervous system activity. Accordingly, treatment must include administration of drugs to stop the central nervous system seizure activity. Benzodiazepines have been generally considered the drugs of first choice because of their efficacy and relative hemodynamic stability. However, propofol is usually more immediately accessible, and it would seem preferable to administer small doses of propofol for seizure suppression when reliance on a benzodiazepine would engender a significant delay in treatment, particularly when there is no evidence of cardiac compromise. Moreover, propofol attenuates anesthetic-induced dysrrhythmias and depression of mean arterial blood pressure during continuous infusion of bupivacaine in rats.\(^8\)
CARDBOVSCLARV 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 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 also produce profound direct cardiac toxicity, and they are not all equivalent in this regard. 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. Such findings support the concept that bupivacaine has greater cardiac toxicity, which has been the driving force for development of single-enantiomer anesthetics, such as ropivacaine and levobupivacaine.

LIPID RESUSCITATION
Recently, a series of systematic experimentation and clinical events have identified a practical and apparently effective therapy for systemic anesthetic toxicity. Based on experiments in rats and dogs, which demonstrated that administration of a lipid emulsion could attenuate bupivacaine cardiotoxicity, intralipid was given to a patient who sustained a cardiac arrest following an interscalene block performed with bupivacaine and mepivacaine. Administration of lipid occurred after a prolonged but unsuccessful attempt at resuscitation using standard Advanced Cardiac Life Support (ACLS) algorithms (also see Chapter 44). The patient subsequently responded to defibrillation, ultimately making a complete recovery. The numerous reports which soon followed provided further support for the efficacy of lipid resuscitation for bupivacaine cardiotoxicity and extended the potential use of lipid rescue for treatment of ropivacaine cardiotoxicity, as well as local anesthetic CNS toxicity. Moreover, experimental work and anecdotal clinical reports also provided evidence that lipid may have utility for treatment of toxicity induced by a wide variety of compounds, such as verapamil, clomipramine, haloperidol, and bupropriion. The mechanism by which lipid is effective is incompletely understood, but its predominant action is most likely related to its ability to extract bupivacaine (or other lipophilic drugs) from aqueous plasma or tissue targets, thus reducing their effective concentration (“lipid sink”). Accordingly, solutions of lipid emulsion should be stocked and readily accessible in any area where local anesthetics are administered, as well as locations where overdoses from any lipophilic drug might be treated. A more detailed discussion of this topic and guidelines for administration can be found in a publication by the American Society of Regional Anesthesia Task Force on Local Anesthetic Systemic Toxicity (asra.com), and at lipidrescue.org. Importantly, propofol should not be administered for this purpose, as the relatively enormous volume of this solution required for lipid therapy would deliver potentially lethal quantities of propofol.

Allergic Reactions
Allergic reactions to local anesthetics are rare, despite the frequent use of these drugs. It is estimated that 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 psychogenic or 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. Although cross-sensitivity does not exist between classes of local anesthetics, 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 ester local anesthetics can receive amide local anesthetics, this recommendation assumes that the local anesthetic was responsible for evoking the initial allergic reaction, rather than a common preservative.

DOCUMENTATION
Documentation of allergy to local anesthetics is based principally on clinical history (e.g., rash, laryngeal edema, hypotension, bronchospasm). However, elevations 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 small advantage with respect to TNS, and spinal procaine is associated with a significantly higher incidence of nausea.15

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.16 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 high doses intended for the epidural space, tempered enthusiasm for neuraxial administration of chloroprocaine. Some early experimental studies attributed this toxicity to the preservative, sodium bisulfite, contained in the commercial formulation.17 However, more recent studies do not demonstrate neurotoxicity from intrathecal bisulfite and even suggest a neuroprotective effect for this compound.18 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.19 Chloroprocaine has been recently reevaluated as a spinal anesthetic,20–22 reflecting clinical concerns related to the possible toxicity of lidocaine placed in the subarachnoid space23 and the low 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 fairly extensive, though published experience to date remains limited. Of note, despite the controversy, chloroprocaine solutions used for spinal anesthesia should be bisulfite-free, and the intrathecal dose should not exceed 60 mg.

Amino-Amide Local Anesthetics

**LIDOCAINE**
Lidocaine is the most commonly used local anesthetic. It is used for local topical and regional intravenous applications, 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.24 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 high doses of anesthetic administered through small-gauge spinal catheters.25 However, even doses of lidocaine routinely used for single-injection spinal anesthesia (75 to 100 mg) have been associated with neurotoxicity.23

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).16,26,27 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,16,26,27 positioning for knee arthroscopy,26 and outpatient status.16 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.16

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. Non-steroidal anti-inflammatory 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 etiology 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 Figs. 11-1 and 11-3). 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. As a spinal anesthetic, it appears to have a low, although not insignificant, incidence of TNS.

PRILOCAINE
Prilocaine was introduced into clinical practice with the anticipation that its rapid metabolism and low acute toxicity (central nervous system toxicity about 40% less than lidocaine) would make it a useful drug. Unfortunately, administration of high 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 IV over 5 minutes). Nevertheless, the capacity to induce dose-related methemoglobinemia has limited the clinical acceptance of this local anesthetic.

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 much lower incidence of transient neurologic symptoms. Although prilocaine is not currently approved for use in the United States, nor is there any formulation available that would be appropriate for intrathecal administration, regulatory approval appears to be forthcoming in Europe.

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, 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. When electrophysiologic differences between anesthetics are compared, lidocaine is found to enter the sodium ion channel quickly and to leave 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 ($V_{\text{max}}$) 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. 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 during high-volume 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. Of note, cardiotoxicity is of no concern when small doses are administered for spinal anesthesia.

Single-Enantiomer Local Anesthetics
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 chier for “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, ropivacaine has a greater propensity to produce vasoconstriction, which may contribute to its reduced cardiotoxicity. In vitro and
in vivo studies provide some support for the reduced cardiotoxicity of ropivacaine compared with bupivacaine. Motor blockade is less pronounced, and electrophysio-
logic studies raise the possibility that C fibers are preferen-
tially blocked, together suggesting that ropivacaine may produce greater differential block. However, as expected from its lower lipid solubility, ropivacaine was found to be less potent than bupivacaine. The question of potency is critical to any comparison of these anes-
thesics; if more drug needs to be administered to achieve a desired effect, the apparent benefits with respect to car-
diotoxicity (or differential block) may not exist when more appropriate equipotent comparisons are made. It appears that ropivacaine 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 bupiva-
caine. 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.

**Eutectic Mixture of Local Anesthetics**

The keratinized layer of the skin provides an effective bar-
ier to diffusion of topical anesthetics, making it difficult to achieve anesthesia of intact skin by topical application. However, a combination of 2.5% lidocaine and 2.5% prilo-
caine cream (i.e., eutectic mixture of local anesthetics[
EMLA]) is available for this purpose. This mixture has a lower melting point than either component, and it exists as an oil at room temperature that is capable of overcom-
ing the barrier of the skin. EMLA cream is particularly useful in children for the prevention or beiin attenuation 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.

**FUTURE LOCAL ANESTHETICS**

Local anesthetics play a central role in modern anesthetic practice. However, despite major advances in pharmacol-
ogy and techniques for administration over the past cen-
tury, 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. Toxicity has been the prominent force behind the evolution of these compounds and the manner in which they are used. Data demonstrate that the neurotoxicity of these compounds does not result from blockade of the voltage-gated sodium channel, indicating that local anesthetic effect and toxicity are not mediated by a common mechanism. Local anesthetic binding to alternative sites at the sodium ion channel may display far greater affinity for neuronal over cardiac channels. The future may see the development of anesthetics with far better therapeutic advantage.

**QUESTIONS OF THE DAY**

1. What is the mechanism of local anesthetic blockade of nerve conduction?
2. Will the addition of sodium bicarbonate hasten the onset of local anesthetic action? Under what circumstances?
3. How does the metabolism of amino-amide local anes-

thetics differ from amino-ester local anesthetics?
4. What are the manifestations of systemic local anes-

thetic toxicity? What are the initial steps in management?
5. Why is bupivacaine associated with greater cardio-

toxicity than lidocaine? What is the mechanism?

**REFERENCES**

12. Rosenblatt MA, Abel M, Fischer GW: Successful use of a 20% lipid emulsion...


