Local Anesthetics

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Historical Perspective

Cocaine, the first local anesthetic, was isolated from leaves of the coca plant, *Erythroxylum coca*, by Albert Niemann in 1860. The medicinal use of coca had long been a tradition of Andean cultures but it was only after chemical isolation that it became readily available in Europe. Its pharmacologic properties after oral ingestion were investigated and described by Sigmund Freud in his publication *Über Coca* in 1884. Freud’s descriptions of the numbing effect of cocaine on skin and mucous membranes prompted his Viennese colleague Carl Koller to use cocaine as a topical anesthetic for cataract surgery, which up until then was performed with the patient awake and associated with severe pain. Toward the end of the 19th century, cocaine was in widespread use for regional and local anesthesia for a myriad of medical indications, and it was also used as a food supplement—for example, in wine and soda beverages. However, the chemical purification of cocaine from coca leaves also increased its toxic and addictive properties, and in the early 20th century the need was identified to synthesize safer medical alternatives to cocaine.

Development of Modern Local Anesthetics

Both cocaine and the subsequent synthetic local anesthetics share as a basic property the reversible blockade of voltage-gated sodium channels. This resulted in two main clinical applications: (1)
Abstract

Local anesthetics are a group of structurally related compounds which share as principal mechanism of action the blockade of voltage-gated sodium channels, resulting in reversible interruption of nerve signal transduction. Currently used local anesthetics are divided into amino amides, or amino esters. Each substance has distinct physicochemical properties, and local anesthetics can be administered continuously or together with adjuvants, allowing clinicians to tailor their anesthetic to procedure and patient. Next to sodium channel blockade, local anesthetics interact with other targets, for example calcium and potassium channels, and G-protein coupled receptors. The latter mode of action explains the anti-inflammatory properties of local anesthetics. Clinical application of existing local anesthetics, and development of novel local anesthetics, is hampered by systemic and local toxicity. Among the additives to local anesthetics, epinephrine is helpful in prolonging duration of action of medium-acting local anesthetics, and to reduce systemic absorption of any local anesthetic. Buprenorphine is an effective additive and has local anesthetic properties but causes excessive nausea and vomiting. Dexmedetomidine and clonidine are popular additives as well but can cause dose-dependent systemic side effects such as sedation, bradycardia and hypotension. Dexamethasone has the least systemic side effects, and the longest prolongation of nerve block duration. Emerging developments in the field of local anesthetics include the development of subtype-specific sodium channel blockers, cell type-specific or heat-assisted delivery, and various modes of encapsulation.

Keywords

local anesthetics
pharmacology
toxicology
pharmacokinetics
pharmacodynamics
reversible interruption of nerve impulse propagation to achieve local or regional anesthesia, and (2) inhibition of cardiac ion channels as a class IB antiarrhythmic agent.

Using cocaine as the basic ester compound, the first derivative, procaine (also known by its trade name Novocaine), was synthesized in 1905. However, procaine was not the optimal local anesthetic because of its very long onset time, short duration of action, and low potency. A breakthrough came in the 1940s when lidocaine (Xylocaine) was introduced. Lidocaine was the first and a prototype compound of the amide class of local anesthetics, which are still in widespread use today. It had fewer undesirable effects than procaine and provided deeper anesthesia. Many new amide local anesthetics were subsequently introduced with differences in speed of onset, potency, and duration of action. Bupivacaine was synthesized in 1957 and rapidly gained popularity because of its long duration of action. However, because of the association of bupivacaine with cardiac toxicity, a less toxic long-acting drug was sought. Bupivacaine is a racemic mixture of the (+) and (−) enantiomers, with lesser toxicity associated with the S(−) form compared with the R(+) form. This led to the development of levobupivacaine and ropivacaine. Today many local anesthetic agents, including both ester and amide types, are available. Although they share the same basic structure, they have distinct physicochemical properties that allow clinicians to choose the optimal anesthetic for specific applications.

Chemical Structure and Physicochemical Properties

All currently available local anesthetics consist of a lipophilic phenyl ring and a hydrophilic tertiary amine joined by an intermediary ester- or amide-based linker (Fig. 20.1).

Ester- Versus Amide-Type Local Anesthetics

Based on the nature of the intermediary chain, clinically used local anesthetics are classified as amino amides (e.g., lidocaine, prilocaine, bupivacaine) or amino esters (e.g., cocaine, procaine, chloroprocaine, tetracaine). Amide and ester local anesthetics differ in their chemical stability, metabolism, and allergic potential. Amides are extremely stable, whereas esters are relatively unstable, particularly in neutral or alkaline solution. Amide compounds undergo enzymatic degradation in the liver, whereas ester compounds are hydrolyzed in plasma by esterases. Cocaine, an ester, is an exception, as it is metabolized predominantly by the liver.

Allergy

True allergy to local anesthetics is rare but is thought to occur more commonly with ester local anesthetics than with amide local anesthetics. The accepted explanation is that metabolites of esters include p-aminobenzoic acid (PABA), which is immunogenic. Some preparations of amino amides contain methylparaben, which has a chemical structure similar to PABA and is a possible allergen in cases of allergic reaction to amide local anesthetics. Preservative-free preparations of local anesthetics are available to address the problems associated with methylparaben. Amide local anesthetics are considered to be one of the safest classes of drugs concerning allergy.

Chiral Forms

With the notable exception of lidocaine, the commonly used amide-type local anesthetics possess one chiral center in the amide piperidine ring. Therefore the plain solution of these substances is racemic, consisting of equal amounts of two possible stereoisomers, which are commonly designated on the basis of geometric configuration as LEVO (left) or DEXTRO (right). These two forms can possess different pharmacologic properties that are of clinical importance. For example, bupivacaine is a racemic mixture, and levobupivacaine is the pure levorotatory enantiomer. Levobupivacaine demonstrates potency and efficacy comparable to bupivacaine but has significantly less cardiac and central nervous system (CNS) toxicity, likely related to reduced affinity for subtypes of sodium ion (Na+) channels expressed in brain and cardiac tissues. Racemic- or R(+)-bupivacaine produces faster and more potent blockade of Na+ channels in swine ventricular cardiomyocytes than levobupivacaine. In addition, racemic or R(+)-bupivacaine produces a greater reduction of the maximum rate of depolarization in animal cardiomyocytes, suggestive of the difference in Na+ conductance.

Physiochemical Properties of Local Anesthetics: Clinical Implications

In general, with increasing length of the carbon backbone, local anesthetics exhibit greater lipid solubility, protein binding, potency, and duration of action. However, these relationships are not linear and are often influenced by multiple other factors. Local anesthetics must penetrate through the lipid-rich nerve sheaths and cell membrane to reach their targets, voltage-gated Na+ channels (Na+). The binding site of local anesthetics is located inside the channel pore and is not readily accessible from the extracellular side as inferred from pharmacologic studies. This concept has gained support from the atomic resolution structure of a bacterial voltage-gated Na+ channel (Fig. 20.2). Therefore local anesthetics must cross the nerve membrane into the cell interior by diffusing through the lipid bilayer to reach their binding site. Consequently, the potency of each local anesthetic is closely related to its lipid solubility and its dependence on pH.

The tertiary amine on the hydrocarbon backbone of local anesthetics is a weak base capable of accepting a hydrogen ion with low affinity to form a conjugated acid. Most local anesthetics have negative logarithm for the acid ionization constant (pKa) values relatively close to but higher than physiologic pH (with some exceptions such as prilocaine, which has a secondary amine
In the subarachnoid space where the nerves lack a sheath, local route of administration and the dose or concentration of drug. Local anesthetics because of the risk of precipitation. Once facilitates translocation of the local anesthetic into the cellular and shifts the equilibrium in favor of the neutral base forms, which neutral lipophilic form than their cationic form. Alkalinization by physiologic pH (7.4), local anesthetics exist in two forms, the positively charged protonated form and the neutral uncharged base form, with the respective ratio described by the Henderson-Hasselbalch equation:

\[
\begin{align*}
\text{pKa} &= \log([\text{H}^+] / [\text{B}^{-}]) \\
\text{pK}_a &= \text{pH} + \log([\text{B}^{-}] / [\text{BH}])
\end{align*}
\]

where B is the base form and BH is the protonated acid form.

Local anesthetics cross the lipid membrane much faster in their positively charged acid and the neutral uncharged base form, with benzocaine that has a primary amine (Table 20.1). Around physiologic pH (7.4), local anesthetics exist in two forms, the positively charged acid and the neutral uncharged base form, with the respective ratio described by the Henderson-Hasselbalch equation:

\[
\begin{align*}
\text{pKa} &= \log([\text{H}^+] / [\text{B}^{-}]) \\
\text{pK}_a &= \text{pH} + \log([\text{B}^{-}] / [\text{BH}])
\end{align*}
\]

where B is the base form and BH is the protonated acid form.

Local anesthetics cross the lipid membrane much faster in their neutral lipophilic form than their cationic form. Alkalinization by sodium bicarbonate addition to local anesthetics increases the pH and shifts the equilibrium in favor of the neutral base forms, which facilitates translocation of the local anesthetic into the cellular interior and speeds onset, but this is not advised for long-acting local anesthetics because of the risk of precipitation. Once inside the cell, the lower pH shifts the equilibrium toward the positively charged protonated form. The charged form antagonizes Na⁺ channels more potently than the neutral form.

The onset of action of local anesthetic action depends on the route of administration and the dose or concentration of drug. In the subarachnoid space where the nerves lack a sheath, local anesthetics are able to reach their targets more readily, leading to a more rapid onset of nerve block with a much smaller dose compared with peripheral nerves. In peripheral nerve blocks, deposition of local anesthetic is in the vicinity of the nerves and the amount of drug that reaches the nerve depends on the diffusion of the drug and the proximity of the injection to the nerve. For a given route of administration, increasing the concentration can accelerate onset. For instance, chloroprocaine is much slower in onset than lidocaine at equal concentrations because its pKa of 9.1 favors the positively charged form at physiologic pH. However, a 3% solution is the typical concentration of chloroprocaine used clinically, which provides a much faster onset than other agents at their clinically used concentrations (e.g., 0.25% bupivacaine, 0.5% ropivacaine, or 1.5% mepivacaine) simply because there are more molecules present to diffuse into the nerve.

The duration of action of local anesthetics is determined primarily by their protein binding (see Table 20.1). Local anesthetics with a high affinity for protein remain bound to the nerve membrane longer. In other words, binding to Na⁺ channels with higher affinity results in a channel blocking effect of longer duration. Duration of action is also influenced by the rate of vascular uptake of local anesthetic from the injection site. The duration of peripheral nerve blocks ranges from 30 to 60 minutes with short-acting agents such as procaine and chloroprocaine to nearly 10 hours with long-acting local anesthetics such as bupivacaine and tetracaine. The rate of vascular uptake significantly affects local anesthetic duration of action as local anesthetics provide their effect as long as they remain at the site of deposition. Therefore deposition of local anesthetics at a highly vascular site such as the intercostal space or inflamed tissue is associated with a higher rate of vascular uptake. Vasocclusion slows the rate of vascular absorption and thus prolongs the duration of action. For this purpose, vasoconstrictive agents such as epinephrine and phenylephrine are frequently added to local anesthetics as adjuvants to increase duration. The prolongation of nerve block with vasoconstrictors is more prominent with local anesthetics of intermediate durations such as lidocaine and prilocaine than with longer-acting agents such as bupivacaine, possibly because the effect of long-acting local anesthetics outlasts that of vasoconstrictors. Local anesthetics themselves tend to have bimodal effects on vascular smooth muscle such that vasoconstriction results at lower doses, whereas vasodilation predominates at higher concentrations with some minor differences between individual agents.

Pharmacodynamics

Nerve Anatomy

The surface of the nerve axon is formed by the cell membrane consisting of a lipid bilayer that contains various proteins, including ion channels. Myelinated nerve axons are surrounded by myelin, produced by Schwann cells, that wraps around the axons to form the myelin sheath. When seen in longitudinal cross section, the myelin sheath is punctuated by gaps called nodes of Ranvier (see also Chapter 8). Other axons such as postganglionic autonomic efferent and some of the nociceptive afferent fibers lack a myelin sheath (Fig. 20.3). Nerves are further organized within three layers of connective tissue: the endoneurium, perineurium, and epineurium (see Fig. 20.3). Nerve fibers are encased in endoneurium, loose connective tissue that consists of glial cells and fibroblasts along with blood capillaries. These fibers are grouped together into fascicles by dense collagenous perineurium. The fascicles are combined to form the peripheral nerve by a thicker layer of epineurium. The
nerves are further encased in fascia. These are the structures that local anesthetics must penetrate to effectively block nerve conduction.

When looking at the sciatic nerve in the popliteal fossa as an example, three further peculiarities become evident. First, the share of nonneuronal tissue (connective tissue, fat, vessels) in peripheral nerves is high, at some locations more than half of the cross-sectional area. Second, while travelling distally, nerve fibers form a plexus in peripheral nerves. Third, before the sciatic nerve bifurcates into the tibial and common peroneal nerve, both nerves can be identified separately inside the thick connective perineurium of the sciatic nerve, at this point sometimes referred to as a paraneural sheath.
Nerves are typically characterized by their degree of myelination, axonal diameter, and speed of impulse conduction (Table 20.2). They are classified as A, B, and C fibers, which roughly correspond to their decreasing cross-sectional diameters. A and B fibers are myelinated, and C fibers are unmyelinated. A and C fibers are further divided into subclasses by their anatomic location and physiologic functions.

**Electrophysiology of Neural Conduction**

The lipid bilayer of the axonal membrane is relatively impermeable to sodium ions but selectively permeable to potassium ions. The electrochemical potential of the cell interior. Resting neural membranes have an electrochemical potential of around $-70 \text{ mV}$. When $\text{Na}^+$ channels open, sodium ions rush inward down the concentration gradient. Other channels, including $\text{Ca}^{2+}$ and $\text{K}^+$ channels, are sensitive to the change in electrical potential and open in response to the depolarization. Neurons are activated by the transduction of chemical, molecular, or thermal stimuli into electrical potential via the influx of cations to raise the electrical potential. The conduction of electrochemical impulses in axons is an *all-or-none* phenomenon. When the depolarization is strong enough, the stimulus is conducted by sequential depolarization of the neural membrane along the axonal length via the opening of $\text{Na}^+$ channels and net inward movement of sodium ions. The sodium ions inside the cell diffuse along the axon in both directions and passively depolarize the adjacent membrane, thereby triggering the opening of additional $\text{Na}^+$ channels by reaching their activation threshold potential. Because the upstream region of the membrane is already depolarized and in a refractory state, the electrical impulse can propagate only in an anterograde direction along the axon (Fig. 20.4A). In myelinated axons, the myelin sheath serves as insulation, and this local phenomenon takes place only at the nodes of Ranvier. Therefore the nerve impulse is able to “skip” the length of myelin to the next node (saltatory conduction), making much faster conduction possible (see Fig. 20.4B). As a rule of thumb, three nodes of Ranvier need to be blocked to reliably interrupt impulse propagation.\(^{22}\)

**Voltage-Gated $\text{Na}^+$ Channels and Their Interaction With Local Anesthetics**

Ion channels are multi-subunit transmembrane proteins that fold in a complex manner to form ion selective pores gated by voltage or ligands (see Fig. 20.2). Ion channels can switch between different conformations in a voltage-dependent manner that determines pore opening (activation), closing (inactivation), and reactivation (to the resting state) (Fig. 20.5). Voltage-gated $\text{Na}^+$ channels consist

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**Table 20.2**

**Different Nerve Types: Characteristics and Sensitivity to Local Anesthetics**

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Diameter (µm)</th>
<th>Conduction Speed (m/s)</th>
<th>Sensitivity to Block</th>
<th>Myelination</th>
<th>Anatomic Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(\alpha)</td>
<td>15–20</td>
<td>80–120</td>
<td>++</td>
<td>+++</td>
<td>Afferent and efferent from muscles and joints</td>
<td>Motor, proprioception</td>
</tr>
<tr>
<td>A(\beta)</td>
<td>8–15</td>
<td>80–120</td>
<td>++</td>
<td>+++</td>
<td>Afferent and efferent from muscles and joints</td>
<td>Touch, pressure, proprioception</td>
</tr>
<tr>
<td>A(\gamma, A\delta)</td>
<td>3–8</td>
<td>4–30</td>
<td>+++</td>
<td>++</td>
<td>Efferent to muscle spindles, sensory roots, and afferent peripheral nerves</td>
<td>Pain, temperature, touch/motor</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>10–15</td>
<td>++++</td>
<td>+</td>
<td>Preganglionic sympathetic</td>
<td>Autonomic—preganglionic</td>
</tr>
<tr>
<td>C</td>
<td>1–2</td>
<td>1–2</td>
<td>++++</td>
<td>–</td>
<td>Postganglionic sympathetic, sensory roots, and afferent peripheral nerves</td>
<td>Pain, temperature, touch</td>
</tr>
</tbody>
</table>

• **Fig. 20.4** Action potential propagates along the axon unidirectionally. The upstream region of the axonal membrane is still in the refractory period and unable to achieve the threshold for depolarization. A, Action potential propagates continuously along the unmyelinated axon by sequential depolarization of the nerve membrane. B, In myelinated axon, the action potential is conducted only at the nodes of Ranvier, skipping the distance between adjacent nodes (saltatory conduction). Na⁺, Sodium ion.

• **Fig. 20.5** Different states of voltage-gated sodium ion (Na⁺) channel. A, Channels in the resting state. Activation leads to opening of the resting (closed) channel (A) to allow the passage of Na⁺ in the activated (open) state (B). The inactivation gate closes the channel pore from the intracellular side and the channel inactivates (D). Local anesthetics (LA) preferentially bind to the activated and inactivated states (C and D). The local anesthetic binding site is in the pore of the channel (C and D).

of a single α subunit and varying auxiliary β subunits. The α subunit forms the ion-conducting pore of the channel and consists of four homologous domains, each with six α-helical transmembrane segments (Fig. 20.6). The loops that connect the S5 and S6 segments of these α helices of each of the four domains are positioned extracellularly and extend inward, which form the narrowest point of the channel pore and are thought to provide its ion selectivity (see Fig. 20.2). In the resting state, the ion pore of the Na⁺ channel is closed (see Fig. 20.5A). Depolarizing voltage changes lead to movement of the voltage sensor (S1-S4) as the result of outward movement of positive charges in the S4 segment, which in turn leads to the rearrangement of S6 segments that results in opening
Na$^+$ Channel Diversity

There are multiple subtypes of voltage-gated Na$^+$ channels arising from variation in the homologous α-subunit genes. The 10 subtypes now known in mammals (Na$_v$1.1 through 1.9 and Na$_x$) are differentially expressed in various tissues with cell- and tissue-specific functions. Sodium channels such as Na$_v$1.8, Na$_v$1.9, and Na$_x$1.7 are expressed exclusively in peripheral neurons. The Na$_v$1.7 subtype determines the ability of nociceptive neurons to transmit noxious stimuli. Rare loss-of-function mutations of Na$_v$1.7 are reported in patients with channelopathy-associated insensitivity to pain, in which patients have selective lack of pain and smell sensation.

of the channel pore (see Fig. 20.5B). The activated channel is inactivated within milliseconds by another conformational change, resulting in the movement of the S6 segment and the S5-S6 linker acting as an inactivation gate (see Fig. 20.5D).

The inactivated state differs from the resting state in its molecular conformation as well as its interaction with local anesthetics, which selectively bind and stabilize the inactivated state. Local anesthetics dose-dependently decrease peak Na$^+$ current through voltage-gated Na$^+$ channels. The binding site for local anesthetics is located interior to the ion-selective pore and can be approached via two different pathways: diffusion of the uncharged form through the cell membrane followed by access to the binding site from the cytosolic side (hydrophilic pathway), and laterally through the lipid membrane (hydrophobic pathway) (see Fig. 20.2B). When bound, local anesthetics stabilize the inactivated state and prevent further activation. They can also bind in the ion channel pore to prevent ion flux (open-state block). Local anesthetics have a higher affinity for Na$^+$ channels in the activated (open) and inactivated (channel pore in open conformation but intracellularly closed by inactivation gate) states than those in the resting closed state (see Fig. 20.5C and D). The difference in the affinity is attributed to the difference in the availability of the two pathways for local anesthetics to reach their binding site. The binding site is more accessible in the activated state than in the resting state.

In the presence of local anesthetics, repeated depolarization results in an incremental decrease in Na$^+$ current until it reaches a newer steady level of inhibition, which is termed use-dependent or phasic inhibition. With repeated depolarization, a greater number of Na$^+$ channels are in the active or inactivated state and are blocked by local anesthetics. Furthermore, the dissociation rate of local anesthetics from their binding site is slower than the rate of transition from inactivated to resting state. Therefore repeated stimulation results in accumulation of local anesthetic–bound Na$^+$ channels, which manifests as use-dependent inhibition or block (Fig. 20.7). The positive charge introduced by the charged local anesthetic is thought to play a minor role.

Na$^+$ Channel Diversity

There are multiple subtypes of voltage-gated Na$^+$ channels arising from variation in the homologous α-subunit genes. The 10 subtypes now known in mammals (Na$_v$1.1 through 1.9 and Na$_x$) are differentially expressed in various tissues with cell- and tissue-specific functions. Sodium channels such as Na$_v$1.8, Na$_v$1.9, and Na$_x$1.7 are expressed exclusively in peripheral neurons. The Na$_v$1.7 subtype determines the ability of nociceptive neurons to transmit noxious stimuli. Rare loss-of-function mutations of Na$_v$1.7 are reported in patients with channelopathy-associated insensitivity to pain, in which patients have selective lack of pain and smell sensation.
On the other hand, several gain-of-function mutations of genes related to the regulation or function of Na\(^+\), result in overactivity of this channel and are associated with the congenital pain disorders (erythermalgia, also termed erythromelalgia) and paroxysmal extreme pain disorder.\(^{29}\) Na\(^{+}\),.7 also appears to be involved in the development of inflammatory pain.\(^{30}\)

**Mechanism of Nerve Block**

It was assumed that only a very small fraction (1%-2%) of local anesthetic reaches the nerve membrane even when placed in close proximity to the nerve.\(^{31}\) With the advent of ultrasound-guided targeting, this fraction might be higher, but still a considerable amount of anesthetic is lost along the concentration gradient across different tissues. The quality of nerve blockade is determined by the potency, concentration, and volume of the local anesthetic. The potency of a local anesthetic can be expressed as the minimum local anesthetic concentration at which complete nerve block is established. The volume of local anesthetic is also important as a sufficient length of axon must be blocked to prevent regeneration of the impulse in the adjacent node of Ranvier. This is understood by the phenomenon of decremental conduction, whereby depolarization of the membrane decays with the distance away from the front of the action potential, and impulse propagation stops when the depolarization falls below the conduction threshold (Fig. 20.8). If less than the critical length of the axon is blocked (usually assumed to be three nodes of Ranvier), the action potential can be regenerated in the proximal membrane segment or node when the decaying depolarization is still above threshold for Na\(^+\) channel activation.

**Other Mechanisms of Local Anesthetic Action**

Local anesthetics block other ion channels besides Na\(^+\) channels, including voltage-gated K\(^+\) channels and calcium ion (Ca\(^{2+}\)) channels, but with lower potency compared with Na\(^+\) channels. Local anesthetics also bind G-protein–coupled receptors and possibly influence the regulation of intracellular Ca\(^{2+}\).\(^{25}\) The significance of these local anesthetic actions is still unclear.

Lidocaine, one of the most studied local anesthetics, also possesses an antiinflammatory effect.\(^{32}\) Lidocaine appears to inhibit release of proinflammatory cytokines and prevent leukocyte adhesion. Some local anesthetics have also been shown to be effective in treating predominantly inflammatory conditions such as irritable bowel diseases (see “Emerging Developments”).

**Difference Between Peripheral and Central Nerves**

Peripheral nerves are covered by a nerve sheath, whereas nerves within the CNS are encased in three layers of meninges: the pia matter, arachnoid, and dura matter. The pia matter is adherent to the nerve itself and separated from arachnoid by cerebrospinal fluid that fills the space between the two layers. This space is the spinal or intrathecal space where “naked” or exposed nerves float in cerebrospinal fluid. The dura matter further outlines the arachnoid membrane, forming a tough covering around the central neuraxis. These meninges taper off as the spinal nerve roots exit the vertebral column via the foramina and course through the epidural space. The presence of these meninges around nerve roots in the epidural space means that 10 times the dose of local anesthetic is required to produce complete nerve block compared with that required in the intrathecal space.

**Differential Block**

Different nerve types show varying susceptibility to nerve block. Table 20.2 displays the characteristics of different nerve types. Clinically, sensory functions are blocked before motor function. This differential nerve block was initially attributed to differences in axon size.\(^{33}\) Furthermore, fiber types do not only differ in myelin sheath thickness and neuron size, but also by functional differences in ion channel composition.\(^{34}\) Noticeptive-selective nerve block (differential block) has been attempted with concentrations of local anesthetics that are just high enough for only certain nerve fibers (smaller diameter, thinly myelinated A\(_o\) or unmyelinated C-fibers), but not for others (larger-diameter, myelinated nerves such as A\(_{\beta}\)). Nevertheless, nerve block does not always follow this size principle in that A\(_\gamma\) is blocked at lower concentration than C fibers and some myelinated fibers before unmyelinated fibers.\(^{35}\) The latter can be explained by the need to block only the nodes in myelinated fibers compared with the whole critical length of the nerve membrane in unmyelinated fibers. Therefore complete pain relief is generally accomplished only with concomitant simultaneous low-threshold sensory sympathetic and motor blockade. Current efforts are targeted at exploring specific nerve blocking mechanisms and developing agents that are more selective or exclusively pain-fiber selective than currently used local anesthetics.\(^{36}\)

**Pharmacokinetics**

The plasma concentrations of local anesthetics are determined by intravascular absorption, distribution, biotransformation, and excretion (Table 20.3). All of these are affected by patient factors such as age, body size, pregnancy and organ function. Therefore clinical data must be synthesized with the pharmacology of the
local anesthetics to predict overall pharmacokinetics in each individual, and to estimate a safe maximum dose for an individual patient (Table 20.4).³⁷

### Absorption

The rate and extent of systemic absorption of local anesthetic depend on multiple factors: site of injection, dose, physiochemical properties of the drugs, and the presence of vasoconstrictive or other adjuvants. Injection in a more vascular tissue results in higher plasma concentration of local anesthetic in a shorter time. Thus a given dose of local anesthetic that can be administered safely for one type of block can result in higher plasma levels and potential systemic toxicity in another type of block. Clinically, the order of decreasing rate of systemic absorption is intravenous, intercostal, caudal, epidural, brachial plexus, femoral, sciatic, and subcutaneous.³⁸ For a specific block technique, the resulting plasma concentration of local anesthetic is generally directly proportional to the dose injected regardless of the concentration of the injectate or the speed of injection. Furthermore, lipid solubility can influence absorption such that more lipid-soluble agents are absorbed more

### TABLE 20.3 Pharmacokinetic Properties of Selected Local Anesthetics

<table>
<thead>
<tr>
<th></th>
<th>( V_{ss} ) (L/kg)</th>
<th>Clearance (L/kg per hour)</th>
<th>( t_{1/2} ) (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine</td>
<td>0.5</td>
<td>2.96</td>
<td>0.1</td>
</tr>
<tr>
<td>Procaine</td>
<td>0.93</td>
<td>5.62</td>
<td>0.1</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1.30</td>
<td>0.85</td>
<td>1.6</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>2.73</td>
<td>2.03</td>
<td>1.6</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>1.2</td>
<td>0.67</td>
<td>1.0</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>1.02</td>
<td>0.41</td>
<td>3.5</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>0.9</td>
<td>0.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.84</td>
<td>0.63</td>
<td>1.9</td>
</tr>
</tbody>
</table>

\( t_{1/2} \), Elimination half-time; \( V_{ss} \), volume of distribution at steady state. Adapted from Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med. 2004;29:564–574.

### TABLE 20.4 Recommended Doses of Selected Local Anesthetics

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset</th>
<th>Recommended Dose (mg/kg)</th>
<th>Maximum Dose (mg) With or Without Epinephrine</th>
<th>Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plain + Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Ester type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fast</td>
<td>10</td>
<td>800</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Fast</td>
<td>10</td>
<td>800</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Epidural</td>
<td>Fast</td>
<td>10</td>
<td>800</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Tetracaine</td>
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<td>Fast</td>
<td>0.2</td>
<td>0.5–6</td>
</tr>
<tr>
<td>Amide type</td>
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<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fast</td>
<td>4</td>
<td>300</td>
<td>0.5–3</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Fast</td>
<td>4</td>
<td>300</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Fast</td>
<td>4</td>
<td>300</td>
<td>1–3</td>
</tr>
<tr>
<td>Epidural</td>
<td>Fast</td>
<td>4</td>
<td>300</td>
<td>1–2</td>
</tr>
<tr>
<td>Topical</td>
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<td>4</td>
<td>300</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Prilocaine</td>
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</tr>
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<td>Fast</td>
<td>8</td>
<td>600</td>
<td>1–2</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Fast</td>
<td>8</td>
<td>600</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Fast</td>
<td>8</td>
<td>600</td>
<td>0.5–3</td>
</tr>
<tr>
<td>Epidural</td>
<td>Fast</td>
<td>8</td>
<td>600</td>
<td>1–3</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Subcutaneous</td>
<td>Fast</td>
<td>5</td>
<td>400</td>
<td>1–4</td>
</tr>
<tr>
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<td>5</td>
<td>400</td>
<td>2–4</td>
</tr>
<tr>
<td>Epidural</td>
<td>Fast</td>
<td>5</td>
<td>400</td>
<td>1–3</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fast</td>
<td>2.5</td>
<td>175</td>
<td>2–8</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Slow</td>
<td>2.5</td>
<td>175</td>
<td>4–12</td>
</tr>
<tr>
<td>Epidural</td>
<td>Moderate</td>
<td>2</td>
<td>170</td>
<td>2–5</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fast</td>
<td>2</td>
<td>150</td>
<td>2–8</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Slow</td>
<td>2</td>
<td>150</td>
<td>14–17</td>
</tr>
<tr>
<td>Epidural</td>
<td>Moderate</td>
<td>2</td>
<td>150</td>
<td>5–9</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fast</td>
<td>3</td>
<td>200</td>
<td>2–6</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Slow</td>
<td>3.5</td>
<td>250</td>
<td>5–8</td>
</tr>
<tr>
<td>Epidural</td>
<td>Moderate</td>
<td>3</td>
<td>200</td>
<td>2–6</td>
</tr>
</tbody>
</table>

slowly than less lipid-soluble ones. This is likely due to sequestration of local anesthetic in lipophilic tissue as well as direct vasoconstriction of vascular smooth muscles by more potent lipid-soluble agents at low doses. The use of vasoconstrictors such as epinephrine reduces the rate of systemic absorption after peripheral and epidural blockade. The rate of distribution can typically be described by a two-compartment model with rapid and slow phases. The rapid phase involves uptake in highly perfused tissues reaching rapid equilibration. For example, the lung is a major site of uptake for local anesthetic. The slow phase depends on the slow equilibration of less perfused tissues and on specific properties of individual local anesthetics.

Distribution
Local anesthetics are distributed throughout the body, but their concentrations vary between different tissue types with preference to more vascular tissues. The rate of distribution can typically be described by a two-compartment model with rapid and slow phases. The rapid phase involves uptake in highly perfused tissues reaching rapid equilibration. For example, the lung is a major site of uptake for local anesthetic. The slow phase depends on the slow equilibration of less perfused tissues and on specific properties of individual local anesthetics.

Metabolism
The major difference between ester- and amide-type local anesthetics is their metabolism. Ester-type local anesthetics undergo hydrolysis by plasma esterases. An exception to this is cocaine, which is metabolized in the liver by carboxylesterase. Amide-type local anesthetics undergo biotransformation mainly in the liver. The rate of metabolism varies between different agents such that degradation of lidocaine is faster than mepivacaine, whose metabolism is still faster than bupivacaine. The metabolites of amide-type local anesthetics are excreted by the kidneys. About 5% of amide type local anesthetics is renally excreted unchanged. Therefore patients with decreased hepatic or renal function eliminate amide-type local anesthetics more slowly and are at increased risk for systemic toxicity. Two notable exceptions are prilocaine, which can be metabolized in the kidney, and articaine, which is inactivated by plasma carboxylesterase.

Toxicity
The toxicity of local anesthetics is the main limiting factor in their clinical applications. Local anesthetics are relatively safe if administered appropriately. However, significant systemic or localized toxicity can result from unintended intravascular, intrathecal, or intraneural injection or if excessive doses are administered, resulting in major systemic absorption.

Systemic Toxicity
The classic cascade of local anesthetic systemic toxicity (LAST) occurs after the administration of a relative overdose of local anesthetic—for example, for a peripheral nerve block, resulting in increased absorption into the systemic circulation and escalating symptoms. These include CNS manifestations, followed by cardiovascular compromise. Other scenarios include inadvertent intravascular injection of local anesthetics, which can cause immediate cardiovascular collapse, and intrathecal injection during neck blocks that causes a short-lived seizure as local anesthetic directly enters the brain. The initial symptoms depend on the plasma concentration of free local anesthetic and patient factors such as acidosis, protein binding, and comorbidities, and vary widely.

Central Nervous System Toxicity
CNS toxicity can manifest from serum concentrations above 5 µg/mL, initially as anxiety, dizziness, circumoral numbness, lightheadedness, and tinnitus caused by blockade of inhibitory brain pathways. The net effect is central disinhibition. Objective symptoms include shivering, muscle twitching, tremors, and eventually generalized tonic-clonic seizure. With a high-dose intravascular injection, a brief period of early symptoms and seizure can be followed by respiratory depression and then arrest. Factors that increase susceptibility to CNS toxicity include use of more potent local anesthetics and the concomitant presence of respiratory or metabolic acidosis (by decreasing the convulsive threshold). Respiratory acidosis also reduces protein binding of local anesthetics, increasing local anesthetic availability for further toxic effects. Elevated partial pressure of carbon dioxide in arterial blood (PaCO₂) leads to cerebral vasodilation and increased delivery of drug to the CNS. However, acidosis promotes amine protonation, leading to less diffusion into nerve cells. In the clinical situation of LAST, normocapnia should be sought.

Cardiovascular System Toxicity
Local anesthetics affect the cardiovascular system both directly by affecting cardiac myocytes and peripheral vascular smooth muscle cells, and indirectly by actions on the CNS or autonomic nervous system. The main mechanisms of cardiovascular toxicity of local anesthetics are blockade of cardiac sodium channels, leading to negative inotropy and arrhythmia. Local anesthetics act directly by decreasing conduction in Purkinje fibers and cardiomycytes by prolonging recovery time. Moreover, fatty acid metabolism is inhibited, leading to energy loss, interference with calcium homeostasis, and disruption of the mitochondrial respiratory chain. The more potent, lipophilic local anesthetics such as bupivacaine, tetracaine, and etidocaine are more cardiotoxic than the less lipophilic agents such as procaine, prilocaine, and lidocaine (see Table 20.1). Specifically, whereas the less lipophilic agents decrease inotropy, the lipophilic local anesthetics such as bupivacaine have an additional antiarrhythmic effect. The dissociation of bound bupivacaine from the local anesthetic binding site is slower (“fast-in,” “slow-out”). Local anesthetics are also direct myocardial depressants via a mechanism related to reduced Ca²⁺ influx and release from the sarcoplasmic reticulum. The action of local anesthetics on peripheral vascular smooth muscle is biphasic with vasoconstriction at low concentrations and vasodilation at higher concentrations. The exception is cocaine, which produces vasoconstriction at any dose.

Indirect cardiovascular effects of local anesthetics are related to the CNS or autonomic system. Patients experiencing the classic cascade of symptoms experience as first cardiovascular symptoms—such as acidosis, protein binding, and comorbidities, and vary widely. The severe cardiovascular toxicity associated with epidural use of 0.75% bupivacaine (and other local anesthetics) in the obstetric population in the late 1970s and early 1980s serves as a prototype example of the public health implications of local anesthetic systemic toxicity. The introduction of epidural analgesia for labor
pain was accompanied by multiple reports of local anesthetic-induced cardiac arrest and death in parturients. These tragic outcomes culminated in the relabeling of bupivacaine by the Food and Drug Administration (FDA), cautioning against the use of high concentrations in the obstetric population and refinement of epidural test dosing techniques. Continued concern about the complications associated with local anesthetic toxicity decades later has resulted in further advancements in treatment, especially lipid rescue.

**Treatment of Local Anesthetic Systemic Toxicity**

Treatment of LAST depends on the detailed symptoms and circumstances of the local anesthetic overdose. The situation is highly dynamic and needs to be reassessed continually until symptoms have resolved. The priority is to maintain cardiocirculatory function and bridge the patient to the resolution of symptoms. When unintentional intravenous injection of local anesthetic is suspected or systemic toxicity is detected, seizures should be interrupted. Depending on the circulatory symptoms, short-acting benzodiazepines such as midazolam or anesthetics such as thiopental or propofol should be administered. Whereas guidelines prefer benzodiazepines because they cause less hemodynamic compromise, it should be considered that their onset of action is substantially longer than with propofol or thiopental. During CNS toxicity, airway management and seizure control are the main priorities. Appropriate monitoring should be applied to assess cardiovascular and pulmonary function. Hypoventilation and respiratory acidosis should be aggressively treated by supplying oxygen or, if needed, establishing a definitive airway and instituting mechanical ventilation. Hypotension and bradycardia should be treated with intravenous fluids and cardiovascular drugs targeted to the signs. Epinephrine is considered the mainstay of immediate treatment, and use of vasopressin has also been suggested. However, literature findings are conflicting as to their benefit, and further studies are warranted. Intravenous administration of lipid emulsion has been used with immediate and successful resuscitation of patients with refractory local anesthetic-induced cardiac toxicity based on multiple case reports and is now a part of standardized treatment algorithms.

The role of antiarrhythmic drugs in local anesthetic induced ventricular arrhythmia is not established. Amiodarone might be the safest option, but during lipid emulsion therapy, it can be sequestered with unpredictable effects. Calcium and sodium channel blockers are contraindicated because they can further depress myocardial function.

**Lipid Rescue**

The first report showing that the infusion of soybean oil emulsion improved resuscitation after bupivacaine-induced cardiovascular collapse in an animal model was published more than a decade ago. Numerous case reports as well as experimental studies have shown the therapeutic effect of intravenous infusion of lipid emulsion in refractory systemic local anesthetic toxicity. The exact mechanism behind lipid rescue is debated. It is currently thought that the main actions involve sequestration of lipophilic local anesthetics and a bolstering of fatty acid metabolism in cardiomyocytes. The clinical relevance of other mechanisms such as direct interactions between bupivacaine and the lipid emulsion at the receptor is unclear. The sequestration hypothesis (“lipid sink”) can also explain the similar antidote effect of lipid infusion for other lipophilic medications, including calcium channel blockers, β blockers, and tricyclic antidepressants. There is a limited number of cases reporting adverse outcomes after lipid rescue, mainly recurrent cardiovascular instability. A theoretical complication of lipid infusion is pancreatitis induced by hyperlipidemia and hyperamylasemia, but it should be considered that lipid administration is often performed in a life-threatening situation such that these theoretical adverse effects should not be weighed too heavily. In addition, careful monitoring of patients for several hours after even successful treatment with lipid infusion is essential as there can be a return of cardiovascular instability as plasma levels of the lipids decline.

**Neurotoxicity and Other Tissue Toxicity**

Direct neuronal tissue toxicity (e.g., transient neurologic symptoms [TNS] and cauda equina syndrome) has been described with multiple local anesthetics, but the incidence appears to be significantly higher with lidocaine and mepivacaine than bupivacaine, prilocaine, and procaine.

TNS is characterized by transient hyperalgesia or dysesthesia in the low back, buttocks, and lower extremities following seemingly uneventful spinal anesthesia but without permanent neurologic damage. Risk of TNS is associated with the use of lidocaine, lithotomy position, and ambulatory procedures. The risk increases with dose, but it does not appear to correlate with the concentration of local anesthetic because there is no difference in the incidence of TNS with 0.5% and 5% lidocaine.

The etiology of TNS is unclear, but both mechanical and pharmacologic factors seem to contribute. Symptoms typically respond to nonsteroidal antiinflammatory drugs.

Direct neurotoxicity can be demonstrated in vitro and in animal models. The potential neurotoxic effects of local anesthetics came to the attention of public health officials in the United States after the introduction of microcatheters for spinal anesthesia in the late 1980s. Reports of cauda equina syndrome associated with typical “spinal” doses of local anesthetic solution injected through microcatheters appeared in the literature. Subsequent investigation using in vitro models of the subarachnoid space revealed that local anesthetic injection through microcatheters resulted in poor distribution and mixing of the drug (i.e., pooling), exposing the nerve tissue to unusually high concentrations of local anesthetic. The incidence of the problem was high enough to culminate in voluntary withdrawal of the microcatheters by the manufacturer.

Today it is accepted that all local anesthetics are neurotoxic, depending on the dose. Over the past two decades, concentrations of local anesthetics have, on average, decreased, and ultrasound has allowed for reduction in local anesthetic dose when applied for peripheral nerve blockade.

**Specific Local Anesthetics**

**Amide Local Anesthetics**

**Lidocaine**

Lidocaine was the first widely used local anesthetic, and is available for infiltration as well as peripheral (including Bier block), spinal, and epidural blocks. Its use for spinal anesthesia has declined due to concerns about neurotoxicity and TNS (see previous text). It can be applied topically as an ointment or jelly, or nebulized as an aerosol to anesthetize the upper airway. Intravenous injection of lidocaine to achieve low plasma levels (<5 µg/mL) results in systemic antiinflammation and analgesia, possibly not only owing to an action in the CNS but also by affecting peripheral nerves or cutaneous nerve endings. Clinically, lidocaine has been
administered as an infusion to treat chronic neuropathic pain and can predict efficacy for oral Na⁺ channel blocking drugs such as mexiletine.⁶²

Lidocaine causes vasodilation at most concentrations; the addition of epinephrine can significantly reduce absorption of lidocaine by nearby vessels, allowing more of the initially administered dose to enter the neural compartment, thereby prolonging the duration of action by as much as 50%.⁶¹ Experimentally, intravenous lidocaine profoundly suppresses both increased peripheral neuronal firing induced by injury and inflammation as well as central sensitization of wide dynamic range neurons in the spinal cord dorsal horn.⁶²

**Prilocaine**
Prilocaine has a clinical profile similar to lidocaine and is used for infiltration, peripheral nerve blocks, and spinal and epidural anesthesia. Because prilocaine causes significantly less vasodilation than lidocaine, addition of epinephrine is not necessary to prolong the duration of action, which can be an advantage when epinephrine is contraindicated. Prilocaine shows the least systemic toxicity of all amide local anesthetics and is therefore useful for intravenous regional anesthesia. However, it causes methemoglobinemia (>500-mg dose) owing to its metabolite o-toluidine, which has significantly limited its use.

**Mepivacaine**
The anesthetic profile of mepivacaine is also similar to lidocaine but with a slightly longer duration of action. However, it is not as effective when applied topically. Although toxicity appears to be less than with lidocaine, metabolism of mepivacaine is prolonged in the fetus and newborn and therefore mepivacaine is not used for obstetric anesthesia. Vasodilation is mild, but adding epinephrine can significantly prolong action.

**Bupivacaine**
Bupivacaine (a racemic mixture of both the R and S enantiomers) provides prolonged and intense sensory analgesia, often outlasting the motor block. For epidural analgesia and anesthesia, bupivacaine is usually used at concentrations from 0.125% (postoperative analgesia) to 0.25% (intraoperative analgesia) to 0.5% (surgical anesthesia), with a 2- to 5-hour duration of action. Peripheral nerve blocks are also performed with these concentrations, depending on the amount of motor block sought. Peripheral blocks can last for 12 to 24 hours. Intrathecal use provides approximately 2 to 3 hours of anesthesia and 4 to 6 hours of analgesia. Other clinical uses include tissue infiltration and “trigger point” injections in treating myofascial pain. Epinephrine is sometimes added as a marker for intravascular injection and to prolong the duration of action owing to decreased vascular absorption. However, as vasoconstriction has less impact on the duration of more hydrophilic agents, epinephrine is more commonly added to more hydrophilic agents such as lidocaine.

LAST following bupivacaine injection is associated with particularly high morbidity and mortality. Its high affinity for Na⁺ channels and high lipid solubility are probably the main causes. On the other hand, lipid emulsion seems to be most effective in treating bupivacaine-induced LAST. By consensus, the 0.75% concentration of bupivacaine is not used in obstetrics because of the associated mortality/toxicity (see above). In many countries, the highest concentration of bupivacaine used now is 0.5%. Because sufficient anesthesia can be achieved with bupivacaine 0.5%, the use of bupivacaine 0.75% does not offer any particular benefits and may be associated with increased local and systemic toxicity.

**Levobupivacaine**
Levobupivacaine is a single-enantiomer preparation consisting of the S enantiomer of bupivacaine. Compared with racemic bupivacaine, levobupivacaine has considerably reduced CNS and cardiovascular toxicity, allowing a larger dose to be given. An animal model demonstration of the lower potential for cardiovascular toxicity associated with levobupivacaine compared with dextro-bupivacaine is shown in Fig. 20.9. The clinical profile and potency of levobupivacaine appears to be similar to that of bupivacaine, with a slightly longer block duration. Levobupivacaine is considered particularly useful when large doses are required, such as for plexus blocks performed without ultrasound guidance.

**Ropivacaine**
Concerns about the cardiotoxicity of bupivacaine led to the development of ropivacaine. Ropivacaine is structurally similar to bupivacaine but was developed as a single, less toxic enantiomer (as with levobupivacaine); it can be administered in larger doses than racemic bupivacaine before early signs of toxicity develop.⁶³ However, if equipotent concentrations/dosages are compared, the difference between bupivacaine and ropivacaine becomes less clear. Overall the clinical profile of ropivacaine is similar to racemic bupivacaine, considering that it is less lipid soluble and less potent than bupivacaine. Epidural application can allow for even greater sensory block without significant motor block (“differential block”). An intrinsic vasoconstricting effect (also true for levobupivacaine) might augment the duration of action and reduce the incidence of cardiotoxicity.

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**Fig. 20.9** Representative changes in the electrocardiogram (lead II) and arterial blood pressure 2 to 3 seconds after infusion of levobupivacaine (L-bupivacaine) or D-bupivacaine (2 mg/kg) in an anesthetized rat. The changes in rhythm and blood pressure are displayed. (Modified from Denson DD, Behbehani MM, Gregg RV. Enantiomer-specific effects of an intravenously administered arrhythmogenic dose of bupivacaine on neurons of the nucleus tractus solitarius and the cardiovascular system in the anesthetized rat. Reg Anesth. 1992;17:311–316.)
## Ester Local Anesthetics

### Procaine

Procaine was used mainly for infiltration and spinal blocks in the early 20th century before lidocaine became popular. However, low potency, slow onset (probably owing to its high pKₐ), and short duration of action limit the use of procaine. Allergic reactions are possible due to the production of the metabolite PABA.

### Chloroprocaine

Because of its relatively low potency and extremely low toxicity, relatively high concentrations of chloroprocaine can be used. It also has an extremely short plasma half-life because it is metabolized rapidly by plasma cholinesterase. Reports of CNS toxicity in the form of seizures are extremely unusual. It is thought to have the lowest CNS and cardiovascular toxicity of all agents in current use. Chloroprocaine is used commonly for epidural anesthesia. It is also used for peripheral blocks in combination with other long-acting, slow-onset local anesthetics for the combined effect of rapid onset and prolonged duration. In obstetrics, epidural chloroprocaine, with or without bicarbonate, is used to attain rapidly surgical levels of anesthesia in preparation for cesarean section. Another theoretical advantage in obstetrics is that there is virtually no transmission of chloroprocaine to the fetus. Epidurally administered chloroprocaine can, however, interfere with the action of subsequently administered epidural amide anesthetics or opioids.

Controversy exists regarding the use of chloroprocaine related to reports of persistent, serious neurologic deficits associated with accidental massive subarachnoid injection (i.e., adhesive arachnoiditis). Initially, the agent itself was implicated, but subsequent evaluation suggested that the preservative antioxidant bisulfite is responsible. However, after elimination of bisulfite a number of reports of back pain have appeared. Recently a renewed interest has actually suggested that bisulfite may be neuroprotective in an animal model.

### Tetracaine

Tetracaine is a slow-onset, potent, and intermediate- to long-acting ester-type local anesthetic. Even longer duration of action can be achieved when tetracaine is administered along with a vasoconstrictor such as epinephrine. However it is quite toxic, and has been suggested to cause neurotoxicity at high doses in animal studies, resulting in cauda equina syndrome with repeated spinal dosing. It is used mainly topically or sometimes for spinal anesthesia. Tetracaine is highly lipid soluble and a significant amount can be absorbed in the mucous membrane or wounded skin.

### Cocaine

The only naturally occurring local anesthetic used clinically is also the only local anesthetic that causes intense vasoconstriction. Thus it is often used as a topical anesthetic (e.g., when anesthetizing the cornea or the nasal airway before endotracheal intubation). Cocaine inhibits the neuronal reuptake of catecholamines and can therefore cause hypertension, tachycardia, dysrhythmias, and other serious cardiac effects.

### Benzocaine

Benzocaine has a slow onset, short duration of action, and is both minimally potent and minimally toxic. Its clinical use is limited to topical anesthesia to anesthetize mucous membranes—for example, to anesthetize the oral and pharyngeal mucosa before fiberoptic endotracheal intubation. Excessive use of benzocaine is associated with methemoglobinemia.

## Mixture of Local Anesthetics

The rationale for the mixture of local anesthetics is an attempt to benefit from their respective pharmacokinetics (e.g., a quick onset with the short-lasting drug while maintaining the long duration of the long-acting drug). However, the beneficial effects of the use of mixtures of local anesthetic agents might be overstated. For example, bupivacaine provides clinically acceptable onset of action as well as prolonged duration of anesthesia. In addition, the use of catheter techniques for many forms of regional anesthesia makes it possible to extend the duration of action of rapid- and short-acting agents such as chloroprocaine or lidocaine. Most importantly, one should be cautioned against the use of maximum doses of two local anesthetics. Toxicities of these agents are independent and should be presumed to be additive. With the advent of ultrasound-guided regional anesthesia, the difference in onset time that can be achieved by mixing local anesthetics is down to a few minutes while losing total block duration at the end, such that this concept may be losing attraction.

## Topical Local Anesthetics

### EMLA

EMLA (eutectic mixture of local anesthetics) cream is a mixture of lidocaine and prilocaine, each at a concentration of 2.5%. It is eutectic because the mixture has a melting point below room temperature and therefore it exists as a viscous liquid, rather than a solid powder. EMLA should be applied to intact skin surfaces because application to breached skin surfaces can lead to unpredictably rapid absorption. It provides dermal analgesia by the release of the lidocaine and prilocaine from the cream into the skin, which leads to blockade of pain transmission originating from free nerve endings. The onset, quality, and duration of dermal analgesia are primarily dependent on the duration of skin application. Although there is considerable interpatient variation, EMLA cream should be applied under an occlusive dressing for about 1 hour to provide adequate analgesia for insertion of an intravenous catheter or the drawing of blood at roughly 2.5 g of the cream applied over a 25-cm² area of skin. Large application area, long duration of application, and impaired elimination can result in high blood concentrations of the local anesthetics. The maximum recommended duration of exposure is 4 hours, although exposures of up to 24 hours have not led to toxic plasma levels of local anesthetics. Caution must be taken in children or very small adults as plasma levels of lidocaine and prilocaine depend on patient size and rate of systemic drug elimination.

### Lidocaine Patch (5%)  

The lidocaine patch (Lidoderm) was approved by the FDA in 1999 for treatment of pain associated with postherpetic neuralgia, a severe chronic neuropathic pain condition. The patch is a topical delivery system intended to deliver low doses of lidocaine to superficially damaged or dysfunctional cutaneous nociceptors in an amount sufficient to produce analgesia without mechanosensory block. Its recommended dosing is an application of up to three patches to intact painful skin areas for 12 hours per day. Pharmacokinetic studies have demonstrated that clinically insignificant plasma levels are achieved with this formulation. The levels are % of those required to produce cardiac effects and ½ of those required
TABLE 20.5 Common Additives to Local Anesthetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Main Mechanism</th>
<th>Common Indication</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>(\alpha_1)-Adrenergic agonism</td>
<td>Peripheral nerve block</td>
<td>3–5 (\mu)g/mL</td>
</tr>
<tr>
<td></td>
<td>Vasoconstriction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(\alpha_2)-Adrenergic agonism</td>
<td>Infiltation anesthesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidural anesthesia</td>
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</tr>
<tr>
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<td></td>
<td>Marker for intravascular injection</td>
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</tr>
<tr>
<td>Opioids</td>
<td>Opioid receptor agonism</td>
<td>Neuraxial block</td>
<td>Intrathecal morphine 100–200 (\mu)g</td>
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<tr>
<td></td>
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<td></td>
<td>Intrathecal sufentanil 5 (\mu)g</td>
</tr>
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<td></td>
<td></td>
<td>Intrathecal fentanyl 10–25 (\mu)g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epidural fentanyl 2–10 (\mu)g/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epidural sufentanil 0.25–1 (\mu)g/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epidural hydromorphone 20 (\mu)g/mL</td>
</tr>
<tr>
<td>Dexmethasone</td>
<td>Unknown</td>
<td>Neuraxial block</td>
<td>Typically not used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripherial nerve block</td>
<td>Dexmethasone 2–4 mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>(\alpha_2)-Adrenergic agonism</td>
<td>Neuraxial block</td>
<td>Up to 1 (\mu)g/kg ideal body weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripherial nerve block</td>
<td>Up to 1 (\mu)g/kg ideal body weight</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>(\alpha_2)-Adrenergic agonism</td>
<td>Neuraxial block</td>
<td>Spinal 10 (\mu)g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripherial nerve block</td>
<td>Epidural 0.5 (\mu)g/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peripherial block 0.5–1 (mcg/kg</td>
</tr>
</tbody>
</table>

Additives

Countless agents have been studied as additives to local anesthetics with the intent to accelerate onset (e.g., sodium bicarbonate) or improve the quality and prolong duration of neuraxial and peripheral nerve blocks (e.g., \(\alpha_2\)-adrenergic agonists, opioids, dexamethasone; Table 20.5). Many substances have been found to enhance peripheral or neuraxial blocks in experimental or preliminary clinical investigations, including ketamine, benzodiazepines, tramadol, tricyclic antidepressants and cholinesterase inhibitors, but they have failed to gain widespread acceptance.

**Nonselective \(\alpha\)-Adrenergic Agonists**

Epinephrine is used as a marker for detecting intravascular injection in both epidural and peripheral nerve blocks. \(\alpha\)-Adrenergic agents also prolong and intensify the nerve block\(^{61}\) owing to local vasoconstriction, which leads to decreased vascular absorption, making more local anesthetic available for nerve block. The extent of block prolongation depends on the specific local anesthetic and the site of injection and is most pronounced with shorter-acting local anesthetics such as lidocaine. Activation of central \(\alpha_2\)-adrenergic receptors in the spinal cord also enhances epidural analgesia by epinephrine and other \(\alpha\)-adrenergic agonists. Epinephrine also decreases neural blood flow, but the clinical relevance of this finding concerning adverse effects is not clear.

**\(\alpha_2\)-Adrenergic Agonists**

Prolongation of nerve blocks by the \(\alpha_2\)-adrenergic agonist clonidine has been the subject of ample research with mixed results. Its effects are mediated through supra spinal and spinal \(\alpha_2\)-adrenergic receptors when used neuraxially, and inhibition of the hyperpolarization-activated cation (I\(_h\)) current has been described in experimental peripheral nerve blockade.\(^{80}\) Higher doses are more effective; for example, 150 \(\mu\)g showed a higher probability of a positive result than 75 \(\mu\)g.\(^{70}\) Some have recommended not to exceed 1 \(\mu\)g/kg body weight to avoid sedative and hypotensive side effects. The effect is more pronounced when clonidine is added to shorter-acting local anesthetics such as lidocaine and mepipvacaine. On average, one can expect 2 to 4 hours of prolongation for peripheral blocks.\(^{71,72}\)

Dexmedetomidine is much more selective for the \(\alpha_2\)-adrenergic receptor compared with clonidine. Dexmedetomidine addition prolongs peripheral nerve blocks by 4 to 6 hours at a typical dose of 1 \(\mu\)g/kg body weight, while systemic administration was less effective. Both clonidine and dexmedetomidine are thought to be safe in terms of neurotoxicity.

**Opioids**

Opioids are also used in neuraxial blocks either alone or in combination with local anesthetics. Intrathecal morphine (0.1–0.2 mg) provides analgesia for up to 20 hours after cesarean section.\(^{73}\) Fentanyl (10–25 \(\mu\)g) improves the spread and prolongs block in spinal anesthesia in a dose-dependent manner.\(^{74}\) Sufentanil (5 \(\mu\)g) produces an effect comparable to 0.2 mg morphine (although much shorter) with a lower incidence of pruritus.\(^{75}\)

Epidural morphine used as an adjunct to bupivacaine or ropivacaine provides effective postoperative analgesia for orthopedic surgeries\(^{75}\) after cesarean section to prolong postoperative analgesia. Respiratory depression is an undesired side effect that can last longer than the analgesic effect and thus mandates monitoring. Epidural fentanyl (2–3 \(mcg/mL\)) is also used as an adjunct to local anesthetics or alone. In general, when administered above the conus medullaris, epidural lipophilic opioids are more effective than intravenous use.\(^{76}\) Lipophilic opioids are also taken up into the systemic circulation, adding a second analgesic mechanism of
action, and it has been suggested by some that the systemic effect explains a substantial share of the clinical effect of lipophilic opioids.77 Nevertheless, fentanyl or sufentanil (0.75–1 μg/mL) is a valuable adjuvant for epidural analgesia with improved analgesia and decreased intravenous opioid requirement.78 Hydromorphone (20 μg/mL), which is less lipophilic than fentanyl or sufentanil, is also an effective adjunct to local anesthetics.79

In peripheral nerve blocks, evidence to support the use of opioids is limited and mostly focused on buprenorphine, a partial opioid agonist with activity at μ, κ, and δ receptors as well as sodium channels.80 Block duration can be increased up to twofold to threefold, but the increase in nausea and vomiting limit its usefulness.71

Dexamethasone

Perineural administration of the antiinflammatory glucocorticoid dexamethasone can prolong both motor and sensory block, although the precise mechanism awaits clarification. Moreover, addition of dexamethasone seems to improve overall analgesia80 and should decrease the incidence of postoperative nausea and vomiting. A currently debated issue is the dose dependency; there seems to be no benefit to add more than 4 mg perineurally.81 Systemic dexamethasone can, within limits, mimic the effects of perineural administration.81 An undesirable effect of dexamethasone is that motor blockade is also significantly prolonged.81 Prolongation of peripheral nerve blocks of up to 10 hours can be achieved. A neurotoxic potential of high perineural doses of dexamethasone has been suggested in preclinical experiments,83 but the clinical relevance and motor blockade is also significantly prolonged.81 Prolongation of peripheral nerve blocks of up to 10 hours can be achieved. A neurotoxic potential of high perineural doses of dexamethasone has been suggested in preclinical experiments,83 but the clinical relevance is unclear because perineural steroid application has been performed for decades in pain medicine without significant untoward effects.

Other Agents

Other agents such as ketamine, tramadol, neostigmine, and midazolam have also been used as adjuvants with favorable results, but data are limited. Some preclinical reports show neurotoxicity,84 and they are not recommended for routine clinical use.

Emerging Developments

Ultrasound and Intraneural Injection

Next to pharmacologic developments, the use of ultrasound has led to a substantial advance in the delivery of local anesthetics, allowing administration of smaller doses while achieving higher success rates. High-resolution surface ultrasound can provide direct real-time imaging of peripheral nerves and identify tissue planes that permit favorable local anesthetic distribution for conduction block and catheter placement. For safe and successful ultrasound-guided neural blockade, one must be familiar with the relevant cross-sectional anatomy and coordination of the imaging probe with the block needle. Real-time and continuous visualization of the procedure needle and the relevant anatomy enhances the safety of needling through structures and the quality of block compared with the blind or nerve-stimulator–guided techniques. If desired, ultrasound guidance can be combined with nerve stimulation to further confirm proximity to neural structures. Nonetheless, the quality of ultrasound-guided procedures is highly operator dependent and requires considerable dexterity and practice.60,65

The high resolution of contemporary ultrasound machines even allows discrimination of intraneural structures such as fascicles. It has been suggested that targeted intraneural but perifascicular injection of local anesthetic offers quick onset of anesthesia,85 and that intraneural injection does not invariably result in nerve damage.87 The latter contention challenges long-held beliefs that intraneural injection must be strictly avoided.88–91 Indeed, for popliteal sciatic nerve blockade in which nerve stimulation is notoriously unreliable, intraneural injections frequently occur without apparent neurologic damage.92 Both preliminary clinical97 and some preclinical93 evidence suggests that it is not as deleterious as once thought. But several factors should be considered. First, local anesthetics are toxic in a dose-dependent manner and intraneural injection theoretically increases the chance of direct toxicity. Second, the nerve contains blood vessels, and bleeding inside the nerve can lead to scarring and permanent loss of function. A potential exception may be the popliteal sciatic nerve block, where local anesthetic can be deposited beneath the thick paraneural sheath but still outside the tibial and common peroneal nerves, resulting in an injection that is in fact intraneural (in the sciatic nerve) but in practice not (outside the two constituent nerves). However, this injection depends on optimal visualization of anatomic structures, perfect block conditions, and a trained team, and it cannot be recommended for broad use. In general, even if intraneural injection does not invariably result in nerve damage, it is not recommended.

Subtype-Specific Sodium Channel Blockers

The observation that ProTX-II, a Na1.1,7-selective antagonist from spider venom, prevents propagation of action potentials in nociceptive fibers suggests that selective Na1.7 blockers might provide a novel target for analgesic therapy.94 Similarly, selective blockade of Na1.8 has been reported to attenuate sensory neuron excitability.95 However, no sensory-selective local anesthetic is currently available, and most contemporary research efforts are directed toward treating chronic pain rather than introducing new local anesthetics.

Cell Type–Specific Delivery

Another possibility is to target local anesthetics to specific cell types in nociception pathways, which has been explored using the permanently charged local anesthetics lidocaine-N-ethyl bromide (QX-314)96 or EN3427.97 Owing to their permanent cationic charge, these compounds do not readily cross the nerve cell membrane, but activation of nonselective ion channels such as the transient receptor potential vanilloid-1 (TRPV-1) receptor creates pores large enough for these compounds to enter the cytoplasm. Because TRPV-1 channels are expressed only on pain fibers, this could allow sensory-specific nerve block, a concept confirmed by several experimental investigations.98 However, QX-314 is more neurotoxic than even lidocaine,98 which hindered further development; neurotoxicity data for EN3427 are not yet available. Furthermore, activation of TRPV-1 requires a nociceptive stimulus such as concomitant application of capsaicin.95 These limitations have precluded clinical introduction of cationic local anesthetics so far.

Heat-Assisted Delivery

Controlled heat-assisted drug delivery (CHADD), a disposable oxygen-activated system that allows controlled release of heat to enhance delivery of local anesthetics, has been used with lidocaine and tetracaine. The formulation is an emulsion in which the active ingredients are in oil phase as a eutectic mixture containing a 1:1
mixture of lidocaine and tetracaine by weight.99 Heat is generated using a mixture of iron powder, activated carbon, sodium chloride, wood flour, and water. The local anesthetics are packed in a shallow chamber below the CHADD patch and sealed in an airtight packet.99 When applied to the skin, the CHADD patch heats spontaneously and increases the temperature of the skin, thereby enhancing permeation of the drugs through the epidermis. The heating element produces a temperature of 39°C to 41°C for 2 hours and reduces the duration of onset compared with other topicaly applied local anesthetics such as a lidocaine/prilocaine combination.100

**Local Anesthetics and the Inflammatory Response**

Local anesthetics have antiinflammatory effects, affecting mainly polymorphonuclear granulocytes (PMNs), but effects on macrophages and monocytes are also implicated.10 Overactive inflammatory responses that destroy rather than protect are critical in the development of a number of perioperative disease states, such as postoperative pain, adult respiratory distress syndrome, systemic inflammatory response syndrome, and multiorgan failure. Some local anesthetics (lidocaine or bupivacaine) reduce formation of leukotriene B4 and interleukin (IL)-1. Leukotriene B4 is a potent local anesthetics (lidocaine or bupivacaine) reduce formation of leukotriene B4 and interleukin (IL)-1. Leukotriene B4 is a potent chemotactic substance. Therefore preventing activation of PMNs is likely to suppress the inflammatory process. Additionally, local anesthetics (ropivacaine and lidocaine) attenuate tumor necrosis factor α and Cα5-dependent upregulation of the CD11b-CD18 complex, surface proteins that allow PMN adhesion to endothelium.102 This is thought to be one of the key mechanisms for the therapeutic effect seen with low-dose topical application of ropivacaine in ulcerative colitis.103 Wound healing is another area of interest in relation to the local anesthetic inhibition of PMN adhesion. But studies have yielded contradictory results such that in vivo investigations have demonstrated delayed wound healing, no effects, or improved wound healing after local anesthetic infiltration.101

Various substances such as tumor necrosis factor, platelet-activating factor, IL-8, lipopolysaccharide, and certain colony-stimulating factors “prime” PMNs for subsequent activation that leads to a potentiated response of PMNs. The mechanism of priming is not fully understood but might play a pivotal role in the overstimulation of inflammatory pathways. Lidocaine and other local anesthetics appear to block the priming of PMNs in a dose-dependent manner.101 This could account for how local anesthetics can decrease tissue damage without significantly inhibiting PMN functions required for host defense.

Another immune-modulating effect of local anesthetics involves impaired release of lysosomal enzymes and inhibition of free radical release from macrophages.104 Macrophage functions of cytokine release, respiratory burst, and phagocytosis are sensitive to intracellular pH changes, and are regulated by vacuole-type H-translocating adenosine triphosphatase (H+-ATPase) and the Na+-H+ exchanger. Local anesthetics inhibit these transporters in human PMNs in vitro.105 Clinically, intravenous application of lidocaine results in a strong antiinflammatory effect that partly replicates the suppression of the surgical stress response seen with epidural analgesia.106 Compared with placebo, lidocaine improves patient outcomes (function, bowel, time to discharge) in visceral surgery patients, while effects in other types of surgery are less clear.107 In addition, antihyperalgesic and antinoiceptive effects have been described, as well as antihypercoagulable effects.12

**Liposomal Formulations**

Liposomes are biocompatible microscopic lipid vesicles with a bilayer membrane structure that can be used to encapsulate and deliver drugs over a longer period. However, tissue reaction to such formulations has been problematic as conventional local anesthetics are intrinsically myotoxic, with increased toxicity over extended durations of exposure. They are also myotoxic when released from a delivery system, even when the delivery systems themselves are minimally toxic.108 In contrast, site 1 sodium channel blockers (like saxitoxin) do not cause myotoxicity or neurotoxicity, which could make them desirable for an extended-release formulation.109 However, these substances are very hydrophilic and thus difficult to encapsulate effectively in polymeric particles. Recently a liposomal formulation using saxitoxin was shown to produce sciatic nerve blockade up to 7.5 days in rats with minimal systemic or local toxicity.110

Liposomal bupivacaine (Exparel) has been approved for wound infiltration in the United States but not in Europe. Early studies support a prolonged mode of action after local infiltration compared with bupivacaine. However, a recent study failed to find a dose-response relationship during femoral block in volunteers such that more clinical research is needed to determine efficacy.111

**Key Points**

- Local anesthetics are classified as ester or amide types based on the linkage between the lipophilic phenyl ring and the hydrophilic amine. This difference is reflected in their physiochemical and pharmacokinetic properties.
- Local anesthetics bind to voltage-gated Na+ channels and block depolarizing Na+ current through these channels.
- Properties such as lipid solubility, protein binding, and pKa of individual local anesthetics affect their speed of onset, potency, and duration of action. Raising the pH of local anesthetic solution favors the membrane-permeable neutral form and accelerates onset of action.
- Voltage-gated Na+ channels transition between resting, activated (open), and inactivated states via coordinated conformational changes. Local anesthetics have higher affinity for the activated and inactivated states than the resting state, leading to use-dependent block.
- There are multiple subtypes of voltage-gated Na+ channels arising from expression of nine homologous α-subunit genes that are differentially expressed in various tissues. Na+ channel subtypes such as Na1.1, Na1.8, and Na1.9 are expressed exclusively on peripheral nerves and play important roles in nociception.
- The rate of systemic absorption decreases from intravenous, intercostal, caudal, epidural, brachial plexus, femoral and sciatic, and subcutaneous administration. The same dose of local anesthetic can result in higher plasma concentration and potential for systemic toxicity depending on the type of block.
• Ester-type local anesthetics undergo mainly hydrolysis by plasma esterases. Decreased activity or absence of plasma cholinesterase can also increase the risk for systemic toxicity with ester-type local anesthetics.

• Amide-type local anesthetics undergo biotransformation mainly in the liver. Their metabolites and about 5% of the unchanged drug are excreted by the kidney. Patients with decreased hepatic or renal function have longer elimination times and are at increased risk for systemic toxicity.

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Physics: Medical Ultrasound

Bradley Stringer and Kai Kuck

OUTLINE

Background
Ultrasound Wave Generation: Transducers, Frequency, Attenuation
Ultrasound Wave–Tissue Interaction: Resolution
Enhancement of Echogenicity
Doppler Ultrasound
Safety of Ultrasound Imaging
Key Concepts

Background

Since the introduction of medical ultrasound imaging systems in the mid-20th century, advances in technology have propelled this point-of-care imaging modality to ubiquitous worldwide use in a multitude of clinical applications. Its low cost, portability, versatility, ease of use, quick results, reasonable learning curve, and safety—coupled with the fact that it does not subject patients and clinicians to ionizing radiation—have made this the first choice for many diagnostic and interventional imaging and therapeutic applications in clinical medicine. To the practicing anesthesiologist, it is useful in many applications, including regional anesthesia, vascular access, airway and lung assessment, transesophageal echocardiography (TEE) and Doppler, focused transthoracic echocardiography (TTE) and transcranial monitoring (e.g., of brain structures and cerebral blood flow.)

All medical ultrasound systems operate in the same basic fashion: High-frequency (pitch) ultrasound waves are generated by and transmitted into the body with an ultrasonic transducer. The sound waves are disrupted as they encounter interfaces between differing tissue types with different echogenicity. Some of the sound energy is reflected back to the transducer, now acting as a receiving antenna, the echoes are analyzed, and an image constructed and displayed using that information.1–6

Ultrasound Wave Generation: Transducers, Frequency, Attenuation

Medical ultrasound systems operate by exciting an array of piezoelectric crystals, causing them to vibrate at an intrinsic resonant frequency. Energy from the vibrating crystals is transmitted into the body in periodic waves of the same frequency. The crystals and supporting electronics and mounting materials are arranged in a pattern such that the sound energy is geometrically focused to a predetermined depth, typically ranging from a few millimeters to several centimeters. The crystals, electronics, and support materials as a functional unit are called a transducer, or probe. Variations in transducer shape, size, and frequency influence the beam pattern of the ultrasonic waves, which dramatically changes the way that the waves interact with tissue and how anatomic images are generated and displayed (Fig. P4.1).

Ultrasound waves will dramatically attenuate in air; there is a small layer of air at the interface between the probe and the patient no matter how firmly the transducer is pressed against the body. To eliminate significant attenuation with dry coupling, all air must be eliminated at the transducer–skin interface by applying a layer of viscous acoustic coupling gel between the skin and transducer before imaging.

Ultrasound Wave–Tissue Interaction: Resolution

As sound waves traverse the body, they encounter tissues of various density and elasticity. Each tissue type conducts sound at a specific speed. The differences in tissue characteristics are intrinsic and result in subtle differences in acoustic impedance, an indicator of the resistance to propagation that the ultrasound wave encounters. According to Snell’s Law, when acoustical energy impinges on tissues of different impedance, an interface mismatch exists and predictable fractions of energy will be transmitted forward deeper into the body, while the balance will be reflected to the transducer as an echo (Fig. P4.2). The energy reflected back to the transducer varies directly with the difference in acoustic impedance encountered by the ultrasound.

The time of arrival and relative strength of the echoes are mathematically analyzed and conclusions about the type, structure, size, density, and movement of the underlying tissues can be drawn. Images are then constructed and displayed (and possibly recorded) for viewing and clinical analysis.

For a given tissue type (and characteristic speed of sound), higher frequencies have shorter wavelengths, as related by the basic wave equation (Eq. 1):

\[ c = \lambda f \]

where

- \( c \) is the constant speed of sound in a given tissue (mm/sec)
- \( \lambda \) is the wavelength of the ultrasound wave (mm/cycle)
- \( f \) is the frequency of insonification (cycles/sec)
The practical application of Eq. 1 is that the resolution of the image is directly proportional to the frequency of the transducer. According to Eq. 1, for a given tissue type with its associated speed of sound, increasing the frequency must be accompanied by a commensurate reduction in the wavelength of the sound. Resolution is inversely related to wavelength (i.e., higher-frequency transducers—hence, smaller wavelengths—typically provide better images than their lower-frequency counterparts). Higher-frequency transducers do suffer from higher attenuation in tissue and cannot penetrate as deeply (penetration is limited to about 200–400 times the wavelength). For example, ultrasound between 2.5 and 7.5 MHz can be used to image structures of 0.4 to 1.2 mm in size and penetrate not more than 24 cm in depth.

**Enhancement of Echogenicity**

The enormously large air–tissue impedance mismatch can be exploited to enhance an image during interventional use such as vascular access and regional nerve blocks. Because needles are typically manufactured with a high polish, the smooth barrel will act like a mirror, reflecting the incoming ultrasound waves away from the transducer and making the needle invisible because no reflective echoes from that structure are received. Because visualizing the needle as it advances into a nerve plexus or vein is critical, in such interventions the needles are often coated in a polymer layer embedded with micro air bubbles, making them extremely diffusively reflective and visible under ultrasonic imaging. In other cases, the polished needle barrel is intentionally etched to a dull finish so that the needle reflects ultrasound waves diffusely, making them more visible (opaque) during the procedure. These various needle modifications are said to be echogenic. Similarly, injectable liquid suspensions of microbubbles of air can be used as ultrasound contrast agents when examining for intracardiac shunts.

**Doppler Ultrasound**

The Doppler effect has important applications in ultrasound imaging and can be used to determine blood flow velocity and direction. The real-world example of sound heard by a stationary observer when a moving train blares its whistle is often used as an example of the Doppler effect. The sound of a passing train whistle is higher in pitch if the train is advancing toward a stationary observer and lower in pitch if moving away. Similarly, the pitch (frequency) of an ultrasound wave is shifted higher or lower as the sound is reflected off a moving anatomic target, usually erythrocytes or heart valve leaflets (Fig. P4.3). The greater the velocity (v) of the target, the greater the Doppler frequency shift:

\[
v = \left( \frac{c_{\text{Ultrasonic}} \times \Delta f}{2 \times f_{\text{Ultrasonic}} \times \cos \theta} \right)
\]

where
- \(c_{\text{Ultrasonic}}\) is the speed of ultrasound in the tissue
- \(\Delta f\) is the Doppler shift in frequency
- \(f_{\text{Ultrasonic}}\) is the original frequency of the ultrasound
- \(\theta\) is the incident angle of the ultrasound beam with respect to the moving object

Blood flow can be calculated from velocity by combining it with the cross-sectional area and an assumption of the velocity profile is made. Also, the Bernoulli equation allows an estimation of the pressure gradient (\(\Delta p\)) across the heart valve:

\[
\Delta p = 4v^2
\]

Important uses of Doppler ultrasound in anesthesiology include TEE, TTE, vascular flow (patency, direction, flow rate, velocity), measurements of cardiac function (output, rate, ejection fraction, regurgitation, and so on), and vascular access (location and discrimination between arteries and veins).

Since many ultrasound systems use color (red, blue, or shades of these colors) to indicate blood flow within the lumen of a vascular structure, the clinician must be aware of how the transducer is oriented with respect to the target blood vessel for two reasons.
The direction of blood flow is relative, so that if the transducer is rotated by 180 degrees and reapplied in the same location, what was first colored red as arterial flow would now be colored blue as venous, and vice versa. Second, the most effective estimation of flow is achieved when the transducer is held at a shallow angle relative to the vessel being scanned. (From Cross ME, Plunkett EVE. Physics, Pharmacology, and Physiology for Anaesthetists: Key Concepts for the FRCA. Cambridge: Cambridge University Press, 2014.)

Safety of Ultrasound Imaging

Unlike radiographic imaging, acoustic radiation is nonionizing and has no known cumulative or immediate adverse effects. It can be used on patients with implanted electronic devices or orthopedic implants. It is useful for patients of any sex or age, including fetal scanning. The safety of clinical staff and observers is assured as well.

Key Concepts

Acoustic Impedance: The resistance to the propagation of ultrasound waves through tissues. Each tissue type has a unique acoustic impedance. Acoustic impedance is the product of the density and speed of sound in the tissue.

Attenuation: The loss of energy of transmitted and reflected sound waves owing to scattering, reflection, refraction, and thermal absorption. Attenuation and frequency are directly related (i.e., higher-frequency sound waves attenuate in the body faster than waves of lower frequency). Attenuation limits the maximum depth of penetration and imaging.

Beam Pattern: The 3-dimensional shape and size of the acoustic energy field applied by the ultrasound probe. The beam pattern varies by probe; each pattern is designed for specific imaging goals.

Frequency: The rate, expressed in cycles per second (unit Hertz [Hz]), at which the patterns of compression and rarefaction pass by a certain reference point. Typical frequencies for medical ultrasound are 2 MHz to 20 MHz, depending on the application. Echocardiography uses frequencies of 2.5 to 7.5 MHz.

Piezoelectric Crystals: These crystals can be used to generate or detect ultrasound waves. A voltage applied across the crystals will produce a pressure field (a stress) on the atoms in their lattice with an accompanying overall contraction or expansion (a strain) in 1 or more dimensions of the material, generating ultrasound waves that emanate from the probe.

Probe: Another name for a transducer (see definition below).

Resolution: A measure of the ability of an imaging system to resolve and display 2 closely spaced reflecting tissue boundaries.

Snell’s Law: A formula describing the relationship between the angle of incidence of a sound wave on a tissue interface and the resultant reflection and refraction of the wave.

Transducer: An array of piezoelectric ceramic crystals and electrical connections with support materials housed in a durable enclosure. The shape, operating frequency, and geometric focus of the transducer are intrinsic and fixed. The transducer emits a pattern of ultrasonic waves and interprets the resultant echoes.

Ultrasound Waves: Regular patterns of mechanical compression and rarefaction traveling in a longitudinal direction in tissue, the frequency of which, by definition, is higher than the human audible range of 20 to 20,000 Hz.

References