Chapter 14

Local Anesthetics

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Introduction

Local anesthetics are a group of chemically related compounds that reversibly bind sodium channels and block impulse conduction in nerve fibers.[1] The interruption of neural transmission in sensory afferent nerves or tracts by a local anesthetic drug after local tissue infiltration, regional nerve blocks, or epidural or intrathecal (subarachnoid) injection uniquely and most effectively prevents or reduces pain or nociceptive input during and after surgery. Analgesia in the desensitized area is not only complete by such techniques, but it also removes the immediate secondary (central) sensitization to pain and reduces the central facilitation of the nociceptive pathway. The use of a local anesthetic is essential if surgery is to be performed in a conscious patient and the pain associated with trauma and inflammation is to be relieved. The use of a local anesthetic technique before surgery may also benefit patients by avoiding general anesthesia or reducing the amount of required general anesthetics. Sustained analgesia into the recovery period is a great benefit to patients when a local anesthetic with a longer anesthetic effect is used. Knowledge of the clinical pharmacology of individual local anesthetics enables the achievement of effective and safe neural blockade. Each of the local anesthetic techniques discussed herein has its own particular rate of onset, duration, and risk of complication.

History

The 100-year history of local anesthetic use in humans has typically involved self-experimentation, followed by widespread application with little testing for electrophysiology and neurotoxicity in animals and humans. Desensitization of a body region dates from 1884, when Koller reported the first topical use of cocaine for rendering the eye temporarily insensible to pain at the Congress of the German Society for Ophthalmology.[2] However, cocaine was found to be extremely toxic and addictive. Einhorn synthesized procaine, the first nontoxic prototype of amino-ester local anesthetics, in 1904. Subsequently, other amino-ester local anesthetics, including tetracaine in 1932 and 2-chloroprocaine in 1955, were synthesized. The next milestone in local anesthetic synthesis was in 1943, when Lofgren developed lidocaine, the prototype for all subsequent amide-type local anesthetics. Within 60 years thereafter, additional amide local anesthetics were produced, including mepivacaine (1956), bupivacaine (1957), prilocaine (1959), etidocaine (1971), articaine (1974), and ropivacaine (1980s).[3,4] Levobupivacaine is the newest member of the

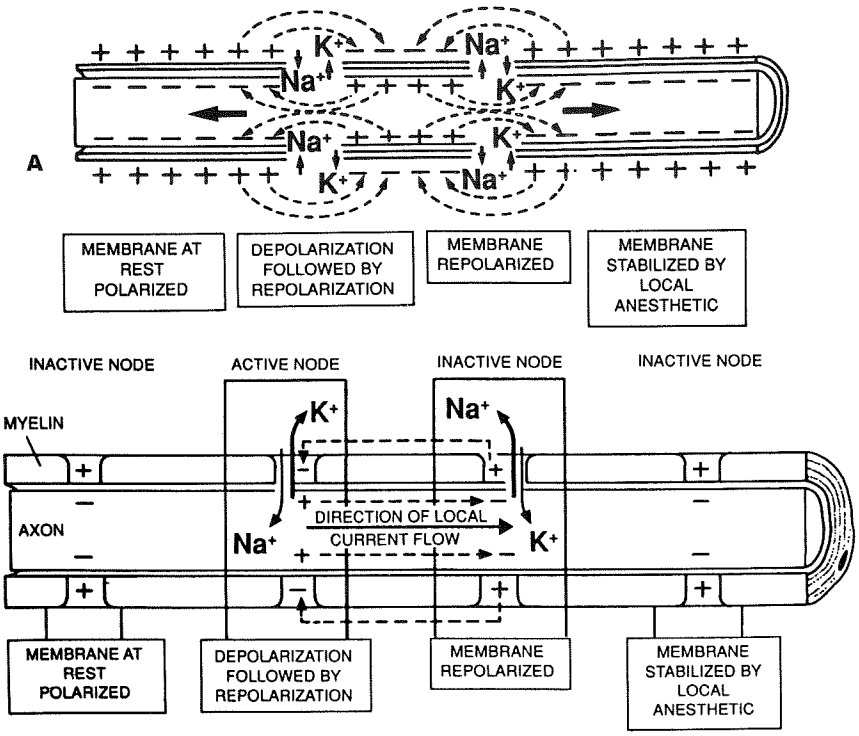


Fig. 14.1. Sodium-ion and potassium-ion flux across the axolemma and propagation of impulse: an unmyelinated nerve fiber **(A)** and a myelinated nerve fiber **(B)**. Reprinted from Skarda,[224] p. 200, with permission from Elsevier.

amino-amide class of long-lasting local anesthetics approved by the Food and Drug Administration (FDA) in 1999.

Electrophysiological Effects

The conduction of impulses in excitable membranes requires a flow of sodium ions through selective sodium channels into the nerve in response to depolarization of the nerve membrane.[5] Mammalian voltage-gated sodium channels consist of one large alpha subunit that contains four homologous domains (D1 to D4), each with six putative α-helical transmembrane segments (S1 to S6) and one or two smaller auxiliary beta subunits.[6] Under resting conditions, sodium ions are at a higher concentration outside than inside the nerve, and a voltage difference across the axonal membrane, known as *resting potential*, of −70 mV exists. When the nerve is stimulated, the permeability of the membrane to sodium ions increases transiently, and sodium passes through the membrane by way of sodium-selective ionic channels that exist in various conformations (i.e., resting, open, or inactivated), depending on the transmembrane potential, depolarizing the plasma membrane. During the depolarization, the action potential moves in obligatory fashion along the axon, allowing for impulse propagation along the nerve membrane (Fig. 14.1). After a few milliseconds, the membrane repolarizes as a result of inactivation or "closing" of the sodium channels. During repolarization, the membrane is no longer permeable to sodium ions, but potassium channels open, and potassium ions flow down their electrochemical gradient out of the cell.[1]

Mechanisms of Action

The precise mode of action of local anesthetic drugs is unknown. A number of theories have been offered: (a) the surface-charge theory (benzene's lipophilic end binds to the membrane hydrophilic end in solution and increases the transmembrane potential), (b) the membrane-expansion theory (benzocaine expands the axonal membrane, compressing the ionic channels), (c) the specific-receptor theory (the biotoxins tetrodoxin and saxitoxin bind to receptors at the external surface at or near the sodium channels, producing a potent conduction block, and (d) the combination membrane-expansion and specific-receptor theory. In this theory, the quaternary ammonium compounds (amides) and ester local anesthetics first pass through the cell membrane as the uncharged base (B) to reach the intracellular site where the uncharged base is protonated and the charged cation (conjugated acid, BH^+) binds to the receptor and "plugs" the channel (Fig. 14.2).[1] Charged or hydrophilic drugs reach the receptor primarily through the open sodium channels and bind more strongly to the closed than open channel. Highly lipid-soluble molecules approach the receptor through the membrane. Perhaps best accepted is the idea that local anesthesia results when local anesthetics bind to sodium-selective ionic channels in nerves, inhibiting the sodium permeability that underlies action potential and depolarization of the cell membrane.[7] Electrical transmission through a myelinated axon stops when enough concentration of the anesthetic is applied to bathe at least three consecutive nodes of Ranvier.[8,9] More recently, local anesthetic binding has been mapped to homologue domains D4 to S6 and inactivation to D3

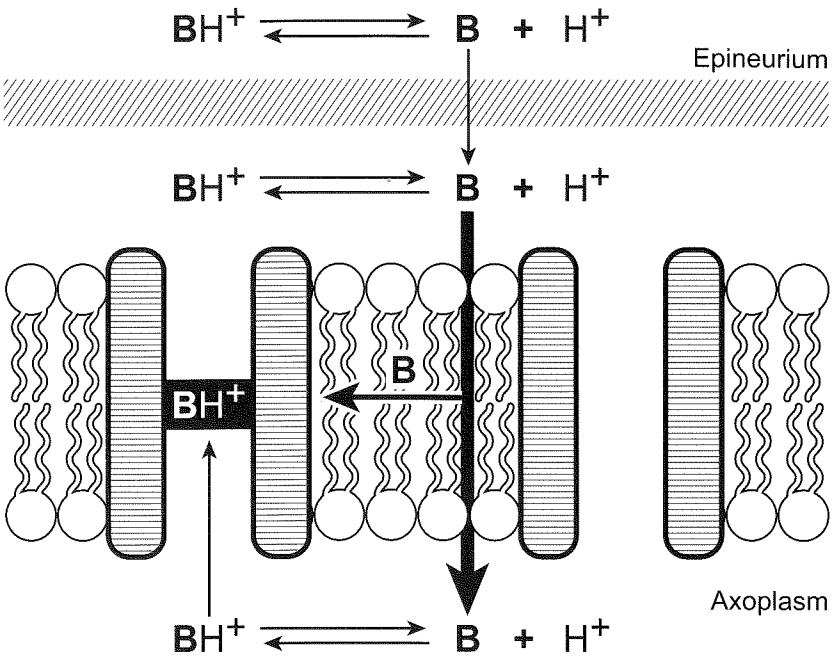


Fig. 14.2. Site of action of amino-ester and amino-amide local anesthetics. The uncharged base form diffuses most readily across the lipid barriers and interacts at the intermembrane portion of the sodium channel. The charged form (BH^+) gains access to a specific receptor via the axoplasmic surface of the sodium channel pore. Modified from Carpenter and Mackey,[76] p. 414, with permission.

to S6 of α-helical transmembrane segments of membrane proteins in sodium channels.[6]

Frequency-Dependent Block

Local anesthetics may differ in their ability to bind to sodium channels, depending on the channel status.[10] Open ion-conducting and inactivated sodium channels have a greater local anesthetic affinity than resting, nonconducting sodium channels. If a frog sciatic nerve preparation is stimulated at low frequency (3 Hz) and exposed to a low concentration of a local anesthetic (1.5 mM lidocaine, 0.125 mM etidocaine, or 0.06 mM tetracaine), a minor decrease in impulse transmission develops. An increase in the stimulus frequency (100 Hz) increases the degree of block.[11] Repetitive stimulation of nerve fibers increases the binding affinity of the receptor site for local anesthetics and facilitates the development of neural blockade, a phenomenon called *use-dependent* or *frequency-dependent block*, or *phasic block*.

Other Mechanisms of Action

Local anesthetics will bind to many different sites that may contain a variety of different sodium channels. The sodium channels in the heart, brain, and axons are not identical.[12] However, if local anesthetics achieve a sufficient tissue concentration, they will affect all excitable membranes, including such as exist in the heart, brain, and neuromuscular junction. The molecular mechanisms by which local anesthetics produce epidural or spinal (subarachnoid) analgesia may include local anesthetic binding to sodium and potassium channels within the dorsal and ventral horns[13] and binding to neural calcium channels, which causes hyperpolarization of cell membranes.[14] Alterations in membrane calcium ion (Ca^{2+}) may be responsible for deformation or expansion of the cell membrane and thus the transmission or conduction of nerve impulses.[15] Local anesthetics may inhibit substance P binding and evoked increases in intracellular calcium (Ca^{2+}),[16] and potentiate γ-aminobutyric acid (GABA)–mediated chloride currents by inhibiting GABA uptake.[17] Spinal anesthesia may also be mediated via complex interactions at neural synapses and disruption of electrical information coding.[18]

Other chemicals, such as toxins, α_2-adrenergic agonists, ketamine, meperidine, calcium-channel blockers, antihistamines, anticholinergics, alcohol, anticonvulsants, barbiturates, and volatile general anesthetics also bind and inhibit sodium channels and often exhibit weak local anesthetic activity.[19–21] Xylazine,[22] ketamine,[23] and meperidine[24] have reportedly produced perineal anesthesia when applied to the caudal epidural space of horses.

Antimicrobial Activity

Additional and sometimes controversial benefits of local anesthetics, which are routinely administered before minor skin surgery and for postoperative pain relief, include both a potent antimicrobial effect[25–27] and improved wound healing.[28,29]

Administration of 1%, 2%, and 4% lidocaine demonstrates a dose-dependent inhibition of growth for all strains of bacteria tested (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*) and no change in the susceptibility of the bacteria to lidocaine by the addition of epinephrine.[26] Likewise, administration of 2% and 5% lidocaine and 1% prilocaine demonstrates a powerful antimicrobial effect on various bacteria, including *Escherichia coli*, *Staphyloccocus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*.[27] In contrast, 0.25% and 0.5% bupivacaine shows poor antimicrobial effectiveness, and ropivacaine has no antimicrobial effect on such microorganisms.

Investigation of the in vivo effects of lidocaine on leukocyte

function in surgical wounds of rats demonstrates lower leukocyte cell counts in the wounds of lidocaine-treated versus placebo-treated rats 48 and 72 h after surgical implantation of hollow titanium implants.[28] At least one histopathological study indicates that local infiltration of 0.5% and 2.0% lidocaine and 0.5% bupivacaine does not substantially alter the healing of midline abdominal incisions in rabbits.[30]

Clinical Pharmacology

Chemical Structure

All local anesthetics contain an aromatic ring at one end of the molecule and an amine at the other, separated by a hydrocarbon chain (Table 14.1).[1,31,32] The aromatic end is derived from benzoic acid or aniline and is lipophilic. The amine end is derived from ethyl alcohol or acetic acid and is hydrophilic. Substitution of alkyl groups on the aromatic ring or amine end increases lipid solubility and potency.

Chirality

In general, local anesthetics are supplied commercially as racemic mixtures of both $R-(+)$ and $S-(-)$ optical stereoisomers. Differences in structure result in various pharmacodynamic and pharmacokinetic actions.

Ropivacaine is provided as the hydrochloride of the pure $S-(-)$ enantiomer.[33,34] It is associated with a reduced incidence of both cardiovascular and central nervous system (CNS) toxicity, a concern with use of racemic bupivacaine.[35] In addition, epidural ropivacaine is similar to bupivacaine in onset, depth, duration, and extent of sensory blockade, although motor block is less intense and briefer.[36]

More recently, levobupivacaine, the pure $S-(-)$ enantiomer of bupivacaine, has been produced. In common with ropivacaine, levobupivacaine is less toxic than bupivacaine, which is attributable to a lesser affinity for brain and myocardial tissue than either that of the $R-(+)$ enantiomer or racemic bupivacaine.[37]

Grouping of Local Anesthetics

The clinically useful local anesthetic drugs essentially segregate into amino esters and amino amides, based on the chemical link between the aromatic moiety and the hydrocarbon chain (Table 14.1). Amino esters have an ester link, and the amino amides have an amide link, respectively. The nature of linkage (ester versus amide) has a notable effect on the chemical stability and the route of metabolism. Ester-linked local anesthetics are cocaine, benzocaine, procaine, chloroprocaine, and tetracaine. Most esters are readily hydrolyzed by plasma cholinesterase and have short half-lives when stored in solution without preservatives. Amide-linked local anesthetics are lidocaine, prilocaine, dibucaine, etidocaine, mepivacaine, bupivacaine, levobupivacaine, ropivacaine, and articaine. The amide agents are very stable, cannot be hydrolyzed by cholinesterase, and rely on enzymatic degradation in the liver. The amide structure of articaine is similar to that of other local anesthetics but contains an additional ester group, which is quickly hydrolyzed by esterases, shortening its duration of action. Ropivacaine and levobupivacaine are synthesized as single $S-(-)$ optical isomers. Other local anesthetics exist as racemates or have no asymmetrical carbons.

The clinical action of local anesthetics may be described by their inherent anesthetic potency, speed of onset of action, duration of action, and tendency for differential block (Table 14.2). These properties do not sort independently.

Local Anesthetic Potency

There tends to be an association between the lipid solubility (octane-water partition coefficient) of a local anesthetic and the local anesthetic potency in vitro.[38] The smaller the molecule and larger the lipophilic property of the local anesthetic, the more readily the anesthetic permeates the axonal nerve membranes, which are highly lipid in composition, and binds sodium channels with greater affinity. The addition of side chains to the lipophilic end of the basic chemical structure increases the lipid solubility and potency of the local anesthetics. The addition of a butyl group to the lipophilic end of procaine forms tetracaine, which is 80 times more lipid soluble and 8 times more potent than procaine. Similarly, replacement of the methyl group with a butyl group on the lipophilic end of mepivacaine yields bupivacaine, which is approximately 30 times more lipid soluble and 8 times more potent than procaine, making it also 15 times more lipid soluble and 4 times more potent than mepivacaine (Table 14.2).

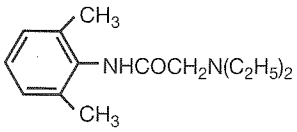
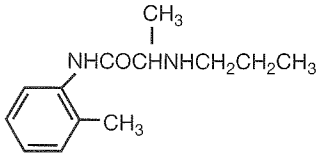
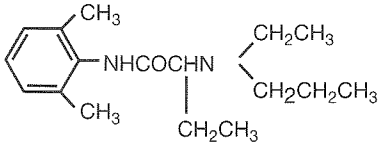
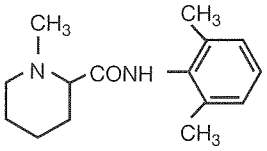
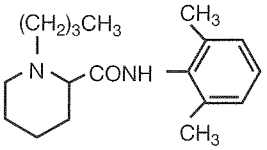
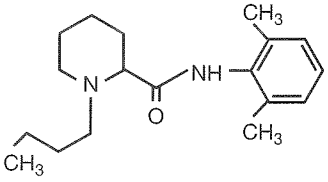
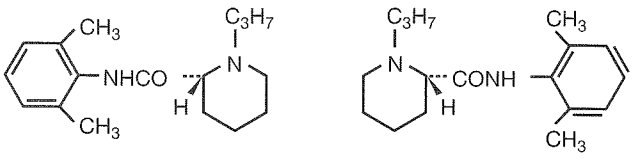
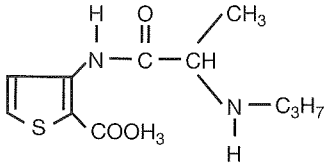
Speed of Onset

The onset of local anesthetic effects in isolated nerves is most likely associated inversely with the lipid solubility and acid dissociation constant (pK_a) of the anesthetic. Most local anesthetics have pK_a values that range from 7.7 to 9.1 (Table 14.2). The percentage of local anesthetic molecules present in the uncharged, nonionized base form, which is primarily responsible for membrane permeability, decreases with increased pK_a at any given tissue pH.[39] When comparing mepivacaine (pK_a, 7.7) with bupivacaine (pK_a, 8.1), mepivacaine with its pK_a nearer to tissue pH 7.4 has a noticeable faster onset of action than bupivacaine (5 to 10 vs. 20 to 30 min). Etidocaine is highly lipid soluble (partition coefficient, 140) and has a low pK_a (7.74), so it penetrates diffusion barriers around A-α nerves relatively easily, producing good motor block within 5 to 10 min. Articaine has good lipid solubility (partition coefficient, 52) and low pK_a (7.8). Articaine (4% solution) produces successful (complete) local anesthesia for periodontal surgery or tooth extraction in 1 to 3 min that lasts for 50 to 60 min.[40] Although chloroprocaine has a higher pK_a than procaine (9.1 vs. 8.9), chloroprocaine is more potent and has a faster onset of action. The pK_a of ropivacaine is 8.07, approximately the same as bupivacaine (8.1) or mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility (partition coefficient of 14 at pH 7.4) compared with bupivacaine (partition coefficient, 30) and mepivacaine (partition coefficient, 2).

Duration of Anesthetic Effect

The duration of clinical local anesthetic action correlates with the high lipid solubility, which also relates to increased potency, as previously described, and to increased protein binding within the axonal membrane and the vasoactivity of the local anesthetic

Table 14.1. Trade names, chemical structure, and main clinical uses of ester-linked and amide-linked local anesthetic agents

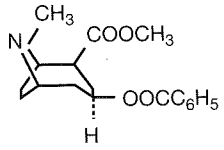
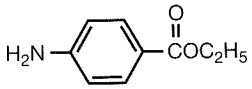
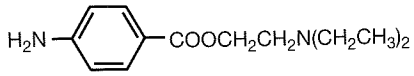
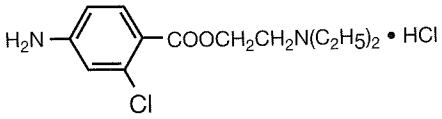
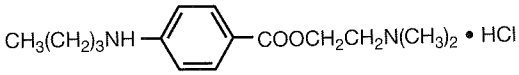
Trade Name	Chemical Structure		Main Clinical Use
Amides			
Lidocaine	Xylocaine Lignocaine		Infiltration, nerve blocks, intra-articular, epidural
Prilocaine	Citanest		Infiltration, nerve blocks, epidural
Etidocaine	Duranest		Infiltration, nerve blocks, epidural
Mepivacaine	Carbocaine		Infiltration, nerve blocks, intra-articular, epidural
Bupivacaine	Marcaine		Infiltration, nerve blocks, epidural, subarachnoid
Levobupivacaine	Chirocaine		Infiltration, nerve blocks, epidural, subarachnoid
Ropivacaine	Naropin		Infiltration, nerve blocks, epidural, subarachnoid
Articaine	Ultracain Carticain		Infiltration, nerve blocks, intravenous, regional anesthesia, epidural

(continued)

drug. Increasing the side chain of the local anesthetic molecule increases the protein binding and prolongs the duration of action. More lipid-soluble local anesthetics are relatively water insoluble and, therefore, highly protein bound (Table 14.2).

The duration of effect of local anesthetics at the site of action is inversely related to the rate of systemic absorption. The rate of vascular absorption varies directly with the vascularity of the injection site and the physicochemical and pharmacological prop-

Table 14.1. Trade names, chemical structure, and main clinical uses of ester-linked and amide-linked local anesthetic agents (*continued*)

Trade Name	Chemical Structure	Main Clinical Use
Esters		
Cocaine		Topical
Benzocaine Americaine		Topical
Procaine Novocain		Infiltration, nerve blocks, epidural
Chloroprocaine Nesacaine		Infiltration, nerve blocks, epidural
Tetracaine Pontocaine Amethocaine		Topical, subarachnoid

erty and dose of the local anesthetic. Lidocaine is a better vasodilator than prilocaine, so lidocaine is removed from the site of injection faster. This makes lidocaine a shorter-acting anesthetic than prilocaine (60 to 120 vs. 120 to 180 min), even though lidocaine is more protein bound (65% vs. 55%).

Articaine is better able to diffuse away through soft tissues and bone than are other local anesthetics, and it contains an ester group, which is quickly hydrolyzed by esterases, shortening its duration to approximately 30 to 45 min.[41] By using articaine in peribulbar anesthesia for cataract surgery, corneal sensation returns quickly, thereby reducing the likelihood of inadvertent damage to an anesthetized eye after discharge.[42]

Tonicaine is a lidocaine derivative compound that produces sciatic nerve blockade with a relatively fast onset (<10 min) and long duration (12 to 16 h). Tonicaine requires additional local and systemic toxicity studies before it can be safely used in animals and people.[43]

Bupivacaine, tetracaine, etidocaine, and ropivacaine are highly lipid-soluble local anesthetics that are only slowly "washed out" from isolated nerves in vitro, and they are not readily removed by the bloodstream from nerve membranes, making their duration of action long (180 to 480 min) (Table 14.2).

Mixtures of Local Anesthetics

Neural blockade produced by mixing of local anesthetics is unpredictable and controversial and may depend on a number of factors, which include not only the types of drugs but also the pH of the mixture. If lidocaine (with fast onset and intermediate duration) and bupivacaine (with long onset and duration of action) are mixed, neural blockade may begin faster and last longer.[44] One study suggests that there is no clinical advantage, with respect to onset and duration of sensory blockade in humans, to using a 50:50 mixture of plain lidocaine (1%) and plain bupivacaine (0.25%) in place of their independent use.[45] Prior administration of chloroprocaine (with fast onset and brief duration) to bupivacaine (with longer onset and duration) shortens the duration of bupivacaine-induced nerve blockade, because the metabolites of chloroprocaine may inhibit the binding of bupivacaine to sodium-channel receptor sites.[46,47] Administration of bupivacaine (2.4 μg/mL) and etidocaine (2.3 μg/mL) causes 38% and 21% inhibition, respectively, of the rate of chloroprocaine hydrolysis by human serum.[48] A mixture of equal parts of 2% chloroprocaine and 0.5% bupivacaine produces a rat sciatic nerve blockade with the characteristics of a chloroprocaine block. Changing the pH of this mixture from 3.6 to 5.6 changes the characteristics to a blockade resembling that produced by bupivacaine.[49] For mixtures of lidocaine-bupivacaine and lidocaine-tetracaine, there is no evidence of a synergistic or antagonistic interaction in rats.[50]

Novel Local Anesthetic Delivery Systems

Vehicles for Sustained Release of Local Anesthetics

Various approaches have been tried to prolong neural blockade and postoperative analgesia for several hours or days after a single administration of a local anesthetic drug. Polyactic, polycar-

Table 14.2. Physical, chemical, and biological properties of currently available local anesthetic agents.

Drug	Lipid Solubility	Relative Anesthetic Potency[a]	pK_a	Plasma Protein Binding (%)	Onset of Action	Duration of Action (min)
Ester linked						
Low potency, short duration						
Procaine	1	1	8.9	6	Slow	45–60
Chloroprocaine	1	1	9.1	7	Fast	30–60
High potency, long duration						
Tetracaine	80	8	8.6	80	Slow	60–360
Amide linked						
Intermediate potency, short duration						
Articaine	52	4	7.8	65	Fast	30–45
Intermediate potency and duration						
Lidocaine	3.6	2	7.86	65	Fast	60–120
Mepivacaine	2	2	7.7	75	Fast	90–180
Prilocaine	1	2	7.7	55	Fast	120–180
Intermediate potency, long duration						
Ropivacaine	14	6	8.07	95	Intermediate	180–480
High potency, long duration						
Bupivacaine	30	8	8.1	95	Intermediate	180–480
Levobupivacaine	31.1	ND	8.09	>97	Intermediate	180–480
Etidocaine	140	6	7.74	95	Fast	180–480

[a]The potency given is relative to procaine. ND, not determined.

bonate, and polymer microspheres containing local anesthetics,[51–53] lecithin-coated methoxyflurane microdroplets,[54] local anesthetics from biodegradable polymer matrices,[55] lecithin-coated tetracaine microcrystals,[56] and liposome-encapsulated lidocaine[57] or bupivacaine[58] have been developed to serve as vehicles for sustained release of local anesthetic agents.

The large unilamellar vehicles (diameter, 300 nm) that exhibit a pH gradient (pH 7.4, outside; and pH 4.0, inside) and encapsulate 0.75% bupivacaine can subsequently provide a sustained-release system that increases the duration of neural blockade from 2 to 6.5 h.[58] In the guinea pig cutaneous wheal model, more than 85% of the liposomal carrier remains at the site of administration for 2 days.[58] The duration of intercostal nerve blockade in sheep increases from 4 to 13 days after using the controlled release of 8 to 80 mg of bupivacaine/kg of body weight and 0.05% dexamethasone from polymer microspheres (470 mg of microspheres containing 352 mg of bupivacaine per nerve).[53]

Continuous Peripheral Nerve Blockade

This can be accomplished by the use of a continuous-catheter insertion system and a disposable infusion pump.[59] Local anesthetic delivery has been applied at the end of surgery on 17 dogs submitted for forelimb amputation, total ear-canal ablation with lateral bulla osteotomy, or median and lateral thoracotomies. The continuous infusion of 2% lidocaine (2 mL/h) into the surgical sites was well tolerated by the patients, producing good postoperative analgesia for up to 50 h, with no acute local anesthetic toxicity, hemodynamic instability, or breakthrough pain.[60]

Differential Nerve Blockade

Controversy still surrounds the differential susceptibility of nerve fibers to local anesthetics and its relation to selective functional deficit. It is apparent that differential block of impulses in nerve fibers exists, varying among different anatomical features (different peripheral nerves, fiber diameter, presence or absence of myelination, and surrounding tissue), different local anesthetics, critical duration of drug exposure (absorption, distribution, and elimination of drug from the site of injection), and different animal species (e.g., frogs, rats, cats, and people).

Sensory and motor fibers have a characteristic neurophysiological profile, motor and sensory function, and conduction-block susceptibility (Table 14.3).

In Vitro Studies

One of the oldest observations about local anesthetic block with cocaine is that dogs and frogs lose sensation before motor function.[61] In vitro studies with desheathed rabbit vagus and sciatic nerve indicate that various local anesthetics (i.e., cocaine, procaine, chloroprocaine, tetracaine, lidocaine, bupivacaine, etidocaine, tetrodoxin, and saxitoxin) block C fibers before A-α fibers.[62] These findings have led to the belief that the susceptibility to local anesthetic depends inversely on fiber diameter. The "size principle" that smaller (slower) axons are always blocked first, however, is not always true. When equilibrium is achieved between the nerve and the local anesthetic solutions, the large A-α fibers are blocked at the lowest drug concentration, the inter-

Table 14.3. Classification of nerve fibers and order of blockade

	Fiber Type					
	A-α	A-β	A-γ	A-δ	B	C
Function	Somatic motor	Touch, pressure	Proprioception	Fast pain, temperature	Vasoconstriction, preganglionic sympathetic	Slow pain, postganglionic sympathetic polymodal nociceptors
Myelin	Heavy	Moderate	Moderate	Light	Light	None
Diameter (μM)	12–20	5–15	3–6	2–5	1–3	0.4–1.5
Priority of blockade	⟵ 5	⟵ 4	⟵ 3	⟵ 2	⟵ 1	⟶ 2
Signs of blockade	Loss of motor function	Loss of sensation to touch and pressure	Loss of proprioception	Pain relief, loss of temperature sensation	Increased skin temperature	Pain relief, loss of temperature sensation

mediate B fibers are blocked at a higher concentration, and the smallest, slowest-conducting C fibers require the highest drug concentration for conduction blockade.[63,64]

Similarly, earlier reports indicate that the larger A-β fibers in rabbit vagus nerve are more susceptible to the local anesthetic blockade than are the small, preganglionic, myelinated B fibers.[64–66] The larger A-δ fibers in the dorsal roots of saphenous nerve of cats are also reported to be more susceptible to procaine blockade than are the C fibers.[63]

In Situ Studies

Local anesthetics have been found to block pain fibers (small unmyelinated C fibers and myelinated A-δ fibers) more readily and before other sensory and motor fibers (large myelinated A-γ, A-β, and A-α fibers) (Table 14.3). Local anesthetics also will block small-diameter myelinated or unmyelinated fibers at a lower concentration than is required to block large fibers of the same type. This is probably attributable to the longer action potentials and the discharge at higher frequencies of smaller fibers.

A recent in vivo electrophysiological study with rats confirmed such results.[67] If the minimal effective threshold concentration of lidocaine in rat sciatic nerve was measured that produced 50% of tonic fiber blockade in large, myelinated A-α and A-β fibers, small myelinated A-δ fibers, and unmyelinated C fibers of sensory axons, and in large myelinated A-α fibers and small A-γ of motor axons, then the order was motor = proprioception (A-γ > A-δ = A-α > A-β fibers) > nociception (C fibers). At 1% lidocaine, all fibers were tonically blocked.

On the other hand, if compound action potentials of the saphenous nerve were recorded before and during blockade with low concentrations with either a low lipid-soluble local anesthetic (e.g., procaine or 2-chloroprocaine) or intermediate lipid-soluble anesthetic (e.g., lidocaine or bupivacaine), then priority of fiber blockade appeared to be C > A-δ > A-α fibers.[68] However, with very lipid-soluble etidocaine, A-δ fibers are blocked before C fibers. Of the local anesthetics tested, 2-chloroprocaine produced the greatest differential rate of block of peripheral nerve fibers, and etidocaine produced the least. Mepivacaine appears to block sensory and motor fibers at the same rate, and bupivacaine and ropivacaine can produce selective sensory analgesia, with little or no motor blockade.[69–71]

Brachial Plexus Infiltration

Deposition of local anesthetics to the brachial plexus of humans has produced either equally fast anesthesia and paralysis by 1% lidocaine or a more rapid motor blockade than sensory blockade by 1% mepivacaine,[72] 0.5% bupivacaine, or 0.5% ropivacaine.[73,74] Similarly, brachial plexus block in dogs produced more rapid onset of motor block when compared with sensory block after the administration of bupivacaine (0.375% with 5 Mg/mL epinephrine, 4 mg/kg) (9.7 vs. 26.2 min, mean values).[75] This phenomenon has been explained by some authors by the somatotopical arrangement of nerve fibers such that the motor fibers would be located at the periphery of the nerve trunk (mantle bundles) and the sensory fibers in the center (or core) (Fig. 14.3).[72,76] Consequently, if sufficient analgesic drug is applied to produce motor blockade, the diffusion of the analgesic or its transport into the nerve by the local blood supply will first affect the motor fibers. However, anatomical studies of the radial, median, and ulnar nerves in humans do not support this concept, making the mechanism for the differential rate of brachial plexus blockade controversial.[77] Analgesia during brachial plexus block in dogs lasted 11 ± 0.5 h in one study, but the relative rates of recovery of motor activity and sensation in dogs after brachial plexus blockade have not been investigated.[75]

Differential Epidural and Spinal Blockade

In general, progression of epidural and spinal anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Exposure of mixed-nerve trunks within the spinal vertebral column to a sufficient concentration of an analgesic drug might cause a loss of sensation in this order: pain, heat and cold, touch, proprioception, and skeletal muscle tone. Recovery of sensation is expected to be in the reverse order.[78]

Autonomic small unmyelinated C fibers and myelinated B fibers seem to be readily desensitized after epidural or spinal ad-

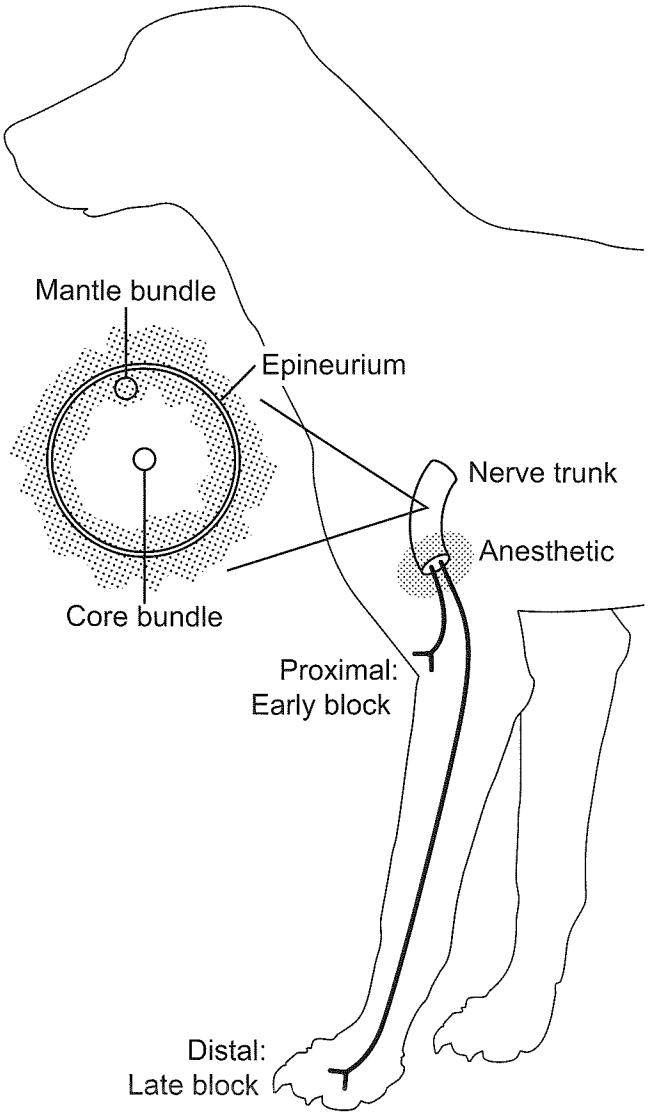


Fig. 14.3. Somatosensory arrangement of nerve fibers in the trunk of the brachial plexus of the dog. Nerve fibers in the mantle or peripheral bundles innervate primarily motor fibers of the proximal limb, whereas nerve fibers in the core or center bundles innervate for the most part the sensory fibers of the distal foot. The concentration gradient that develops during initial diffusion of local anesthetic into the nerve trunk causes onset of anesthesia to proceed from proximal to distal. Recovery from anesthesia also proceeds from proximal to distal because of absorption of local anesthetic into the circulation surrounding the nerve trunk.

ministration of local anesthetics. Spinal anesthesia is generally characterized by preganglionic sympathetic nerve blockade (B fibers) that extends further than sensory block (A-δ fibers), and sensory block extends further than somatic motor block (A-α fibers).[79]

The relative importance of blockade of each class of fiber (A-β, A-δ, and C) for surgical anesthesia has been assessed by measuring cutaneous perception thresholds in people. In this study, A-β, A-δ, and C fibers of the skin were stimulated at 2000, 250, and 5 Hz, and demonstrated differential block by the sequential return of sensation to touch (A-β function), then pinprick (A-δ function), and lastly cold (C-fiber function), respectively.[80]

Sensory anesthesia sufficient for surgery usually cannot be obtained without motor impairment. Adequate sensory analgesia with little or no motor blockade can be achieved with the epidural administration of low concentrations of bupivacaine or ropivacaine combined with opioids and/or α_2-agonists. Epidural blockade may be able to differentiate between sympathetic, somatic, and central pain in patients with chronic pain.

Factors Influencing Anesthetic Activity

A variety of factors can influence the quality of regional anesthesia, including the local anesthetic dose, site of administration, additives such as epinephrine or hyaluronidase, pH adjustment and carbonation, baricity, temperature, mixtures of local anesthetics, and pregnancy.

Dose of Local Anesthetic Agent

A greater dose (volume and/or concentration) will facilitate overall efficacy, thereby decreasing the delay of onset of action and increasing both the likelihood of successful anesthesia and its duration. The potential of systemic toxicity by inadvertent intravenous injection of an anesthetic,[81] or neurotoxicity after inadvertent subarachnoid injection,[82] precludes the routine administration of larger doses of local anesthetic.

All local anesthetics can be neurotoxic, particularly in concentrations and doses larger than those used clinically. Large-scale surveys, using histopathological, electrophysiological, behavioral, and neuronal cell models, indicate that lidocaine and tetracaine seem to have a greater potential for neurotoxicity than does bupivacaine at clinically relevant concentrations administered intrathecally (spinal).[83]

Volume of Local Anesthetic

Generally, a larger volume of local anesthetic will produce a faster and denser block. An exception to this rule is articaine, which readily penetrates tissues and produces anesthesia in approximately 2 min, irrespective of the volume injected. The necessity of a larger injected volume of anesthetic solution for a high rate of complete sensory block can be minimized during axillary plexus blocks in people[84] and dogs[75] if an adequate concentration of a local anesthetic agent (e.g., 1% mepivacaine or 0.375% bupivacaine) is precisely administered at multiple injection sites covering all major nerves of the brachial plexus.

Administration of large volumes (0.22 to 0.33 mL/kg) of bupivacaine (0.75%), lidocaine (2%), or 2-chloroprocaine (3%) into the subarachnoid space of sheep and monkeys has produced neurological deficits and histological abnormalities of the spinal cord, but no one local anesthetic was considered more neurotoxic than another.[82]

Concentration of Local Anesthetic

A higher concentration of local anesthetic will also produce a faster and denser block. Increasing the concentration of lidocaine

and bupivacaine during phasic ("use dependent") inhibition of sodium currents increases the rate of binding but has no effect on unbinding sodium channels.[85] In general, the chance for successful desensitization and anesthesia decreases when the concentration is lowered. One study suggests that lumbar epidural anesthesia with 10 mL of 2% lidocaine in humans produces more intense blockade of large-diameter and small-diameter sensory nerve fibers than that with 20 mL of 1% lidocaine.[86] Similarly, administration of 0.75% ropivacaine into the lumbar epidural space of dogs produces a higher rate of complete anesthesia than does 0.5% ropivacaine of similar volume (0.22 mL/kg).[87]

Injection Site

In general, the fastest onset (within 3 to 5 min) and shortest duration (1 h) of anesthesia is usually produced after subcutaneous and intrathecal injections of 2% lidocaine or mepivacaine hydrochloride solution, followed in order of increasing onset time for minor nerve blocks (5 to 10 min), major nerve blocks, and epidural anesthesia (10 to 20 min).

Additives

Vasoconstrictors

As a general rule, the addition of a vasoconstrictor to a local anesthetic agent, such as epinephrine, allows for decreased local perfusion, delayed rate of vascular absorption of local anesthetic, and therefore increased intensity and prolonged anesthetic activity. Lumbar epidural anesthesia, using 10 mL of 1% lidocaine with epinephrine 1:200,000 produces a more intense block of both large-diameter and small-diameter sensory nerve fibers than that achieved with lidocaine alone.[88]

The usual concentration of epinephrine is 5 μg/mL or 1:200,000 (1 mg/200 mL of saline), which may be obtained by adding 0.1 mL of 1:1000 (0.1 mg) epinephrine to 20 mL of local anesthetic solution. Alternatively, 1:1000 epinephrine may be diluted with preservative-free normal saline. The maximum safe concentration of epinephrine is 1:50,000; concentrations less than 1:200,000 are less effective.

Market preparations of local anesthetics that contain epinephrine 1:200,000 have a lower pH (to retard oxidation) than do plain solutions; for example, 2% lidocaine without and with epinephrine 1:200,000 has a pH of 6.78 and 4.55; and 0.5% bupivacaine without and with epinephrine (1:200,000) has a pH of 6.04 and 3.73, respectively. The pH of solutions freshly prepared with epinephrine is higher than the pH of commercial preparations containing epinephrine; for example, the pH of 2% lidocaine and 0.5% bupivacaine with freshly added epinephrine 1:200,000 is 6.33 and 5.99, respectively. The low pH of the epinephrine preparations will potentially decrease the amount of free protonated anesthetic base available for diffusion through the axonal membrane, thereby slowing the onset of action.

Epinephrine effects depend on the injection site and the local anesthetic, but, in general, it reduces the potential toxicity of local anesthetics by causing vasoconstriction and thus preventing higher blood concentrations.[89] Epinephrine (1:200,000) reduces the average anesthetic blood concentration in dogs given an epidural injection of either 3 mL of 1% ropivacaine or 0.75% bupivacaine at various time intervals, but not the time to achieve maximal blood levels, and it does not alter onset or duration of sensory or motor blockades produced by epidural ropivacaine 1% or bupivacaine 0.75% in dogs.[90]

Acidic epinephrine-containing local anesthetic solutions can decrease the pH at the site of injection, depending on the buffer demand of the injectate and the buffer capacity of the tissue. Epinephrine should not be added to local anesthetics intended for nerve blocks that have an erratic blood supply and for intravenous regional anesthesia with use of a tourniquet because it can cause nerve ischemia and prolonged blockade. Epinephrine often causes tissue necrosis along wound edges. Lidocaine, bupivacaine, and etidocaine equally protect against epinephrine (5 μg/kg/min)-induced arrhythmias in dogs anesthetized with a 1.4 minimum alveolar concentration of halothane.[91] Norepinephrine and phenylephrine appear to have no clinical advantage over epinephrine.

Hyaluronidase

This depolymerizes hyaluronic acid, the tissue cement or ground substance of the mesenchyme, aiding in the local anesthetic spread of an anesthetic agent.[92] The addition of hyaluronidase 3.75 IU/mL to 2% lidocaine, 0.75% bupivacaine, or a 1:1 mixture of 0.75% bupivacaine and 2% lidocaine is reported to improve the diffusion of local anesthetics, resulting in more effective retrobulbar-peribulbar anesthesia and extraocular muscle akinesia after retrobulbar injections.[93,94] Increasing the concentration of hyaluronidase to 7.5 IU/mL does not provide any further advantage over 3.75 IU/mL. The increased permeability of tissues may enhance systemic absorption (and toxicity) but shortens the duration of anesthetic effects because more drug is available in base form. The addition of 5 IU of hyaluronidase/mL of 1% lidocaine with 1:200,000 epinephrine solution in a standard dose and technique for ophthalmic surgery (2 mL as retrobulbar injection for intraocular anesthesia, 2 mL for upper-eyelid anesthesia, and 4 mL for extraorbital facial nerve blockade) reportedly does not increase the systemic absorption and cerebrospinal fluid (CSF) concentration of lidocaine in dogs.[95] However, administration of hyaluronidase does not seem to enhance the efficacy of newer local anesthetics with improved spreading power (e.g., articaine and ropivacaine). Administration of 2% articaine or 1% ropivacaine produces a faster onset of anesthesia and less pain on injection than does administration of 1% bupivacaine.[42,96] Hyaluronidase is a protein that cannot be heat sterilized.[97]

pH Adjustment and Carbonation

The pH of the local anesthetic solution affects the local distribution of the anesthetic. Extracellular increase of bicarbonate increases the cross-membrane pH gradient, the intracellular concentration of the ionized local anesthetic, and local anesthetic effects.

The addition of sodium bicarbonate to procaine, chloroprocaine, mepivacaine, or lidocaine will shorten the onset of nerve block, enhance the density of block, and prolong the duration of block in isolated nerve preparations.[98] This is likely because the amount of nonionized base increases, which enhances diffusion

of the local anesthetic through axonal membranes and ion trapping due to the increased cross-membrane pH gradient.

The efficacy of alkalinization depends on the local anesthetic and regional block techniques. The addition of sodium bicarbonate for median nerve block in humans decreases the pain on injection and increases the rate of onset of motor block, but has no effect on duration of sensory anesthesia.[99] Similarly, adjusting the pH of 1% lidocaine or 0.25% bupivacaine with sodium bicarbonate to 7.4 has little effect on duration of anesthesia after injection into the infraorbital area or abdominal musculature.[100]

In humans, alkalinization produces the best results with 2% lidocaine and 0.5% bupivacaine for epidural block, with 2% lidocaine for axillary brachial plexus block, and with 2% mepivacaine for sciatic and femoral nerve blocks.[101] Bicarbonate has minimal effects when added to ropivacaine.

Increasing the pH of lidocaine or mepivacaine from 4.5 to 7.2 by adding 1 mEq of sodium bicarbonate/10 mL of local anesthetic before injection has been shown to accelerate the onset of epidural anesthesia in humans.[102,103] A pH increase of 2% 2-chloroprocaine from 7.1 to 7.7 with sodium bicarbonate accelerates epidural anesthesia in humans, but a pH increase from 7.1 to 7.7 with tromethamine does not, indicating that factors other than just pH are responsible for the more rapid onset of anesthesia.[104]

Local anesthetic solutions may deteriorate with time upon addition of bicarbonate. Solutions of lidocaine and 2-chloroprocaine readily alkalinize to near physiological pH without precipitation. Mepivacaine 1.5% precipitates above neutral pH within 20 min. Bupivacaine and etidocaine precipitate after the addition of small amounts of sodium bicarbonate and cannot be alkalinized to physiological pH.[105] The mixtures should be used within 20 min of their preparation.

The addition of carbon dioxide to lidocaine produces a more rapid onset and better quality of epidural anesthesia in humans.[106] Marketed solutions of carbonated lidocaine have an adjusted pH ranging from 6.35 to 6.9, and the PCO_2 is 700 mm Hg.[102] Opening the vial lets the carbon dioxide escape, thereby increasing the pH to above 7.0.

The use of carbonated lidocaine for epidural anesthesia in horses did not demonstrate the theoretical expectations of increased diffusion and faster onset of perineal anesthesia.[107]

Baricity

This is defined as the calculated ratio of the density of a solution to the density of CSF. One of the most important physical properties affecting the spread of local anesthetic solutions and level of analgesia achieved after intrathecal administration of a local anesthetic is its density relative to the density of CSF at 37°C.[108]

Density is the weight of a unit volume of solution (grams per milliliter) at a specific temperature, whereas the *specific gravity* (SG) is the calculated ratio of the density of a solution (x) to the known density of water (y), ($SG = x/y$). The density of a drug in solution cannot be determined from a simple formula because it depends on the physical state of that substance in solution.[109] The density of intrathecal agents is usually compared with the density of the CSF. At room temperature, most glucose-free drugs are isobaric with respect to CSF, but as drugs warm to body temperature they become relatively hypobaric. The densities of 2% lidocaine and 0.5% and 0.75% bupivacaine, for example, are slightly less than that of normal range of CSF in humans and therefore can be considered slightly hypobaric.[110] The density of 0.2% tetracaine is the same as water (0.993 g/mL). Continued dilution of 0.75% bupivacaine with water produces increasingly hypobaric solutions. The 0.075% bupivacaine (1:9 dilution) has a density comparable to that of water (0.993 g/mL).[111]

Hypobaric solutions have a baricity less than that of CSF and will migrate to nondependent areas during and immediately after the injection. Glucose-free 0.5% bupivacaine acts as a hypobaric solution, which produces a higher level of analgesia in the nondependent side compared with the dependent side in patients positioned laterally.[112] The unpredictability of extent of spinal block provided by spinal bupivacaine (0.5%) and tetracaine (0.5%) in humans may be related to individual variations in CSF densities.[113] Humans with higher CSF densities demonstrate a higher spinal block after administration of plain bupivacaine (0.5%, 3 mL).[114]

Dextrose and hypertonic saline–containing local anesthetic solutions (e.g., tetracaine in 10% glucose, and dibucaine in 5% hyperbaric saline) have a specific gravity greater than that of CSF. They will migrate from the site of injection to dependent areas.[115] Hyperbaric solutions are created by combining local anesthetics (e.g., 0.5% bupivacaine or 0.5% ropivacaine) with an equal volume of 10% dextrose, producing final drug and dextrose concentrations of 0.25% and 5%, respectively.[116] Lidocaine (1.5%) in 7.5% dextrose in water is clinically indistinguishable from 5% lidocaine in 7.5% dextrose in water as a spinal anesthetic for lower abdominal surgery in humans.[117]

Local anesthetic agents and solvent solutions often contain additives, which affect pH, osmolality, preservation, and vasoconstriction, that may in turn alter the density and specific gravity of the local anesthetic and, therefore, spread of spinal anesthesia.[118] CSF pH and the addition of vasopressors (0.2 mg of epinephrine or 2 mg of phenylephrine) minimally affect the onset of spinal anesthesia with 10 mg of tetracaine and 1 mL of 10% dextrose. However, the addition of epinephrine or phenylephrine at these doses prolonged spinal anesthesia by 53% and 72%, respectively.[119]

Temperature

The cooling of mammalian nerves in vitro slows the conduction velocity and increases the susceptibility to local anesthetic inhibition of transmission.[120] The potency of local anesthetics increases in vitro and in vivo with cooling in some instances but not in others. Inhibition of C fibers (as assessed by galvanic skin potentials) is marginally faster when ice-cold lidocaine (1%) is used compared with room-temperature lidocaine (1%) for median nerve blocks in volunteers.[121] Cooling of lidocaine increases its pK_a and the relative amount of the protonated (active) form within lipid, thereby potentiating the anesthetic effect.[122] On the other hand, a decrease in temperature from 37° to 20°C decreases the uptake of lidocaine in mammalian sciatic nerve by 45%. It is unlikely that cooling of local anesthetics (5°C) before injection of small volumes (5 mL) will be of any effect under clinical condi-

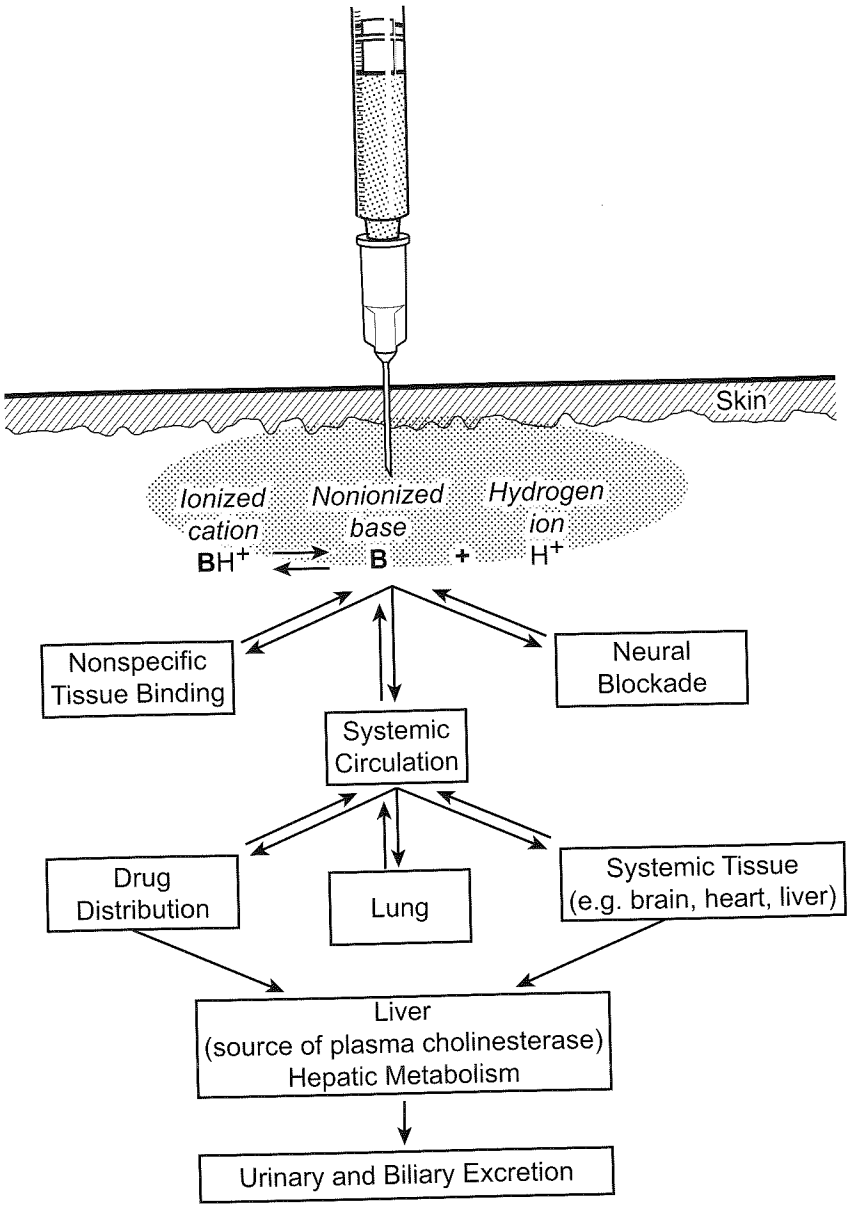


Fig. 14.4. Factors that determine the diffusion of local anesthetic near the site of injection and within the body. The nonionized base of the anesthetic (B) diffuses into the axon and nonspecific tissues. Nonspecific tissue binding and absorption into the bloodstream reduce the mass of drug available to diffuse into neural tissue. Further explanation is under the Drug Disposition section.

tions because of rapid warming of the local anesthetic by the surrounding tissue, preventing the nerve itself from growing cold.[123]

Pregnancy

This appears to increase the susceptibility of nerves to local anesthetics. Pregnant women with lidocaine (1%)-induced median nerve block at the wrist have a greater decrease in sensory nerve action potential than do nonpregnant women, indicating that pregnancy increases median nerve susceptibility to lidocaine desensitization.[121] Similarly, isolated vagus nerves removed from pregnant rabbits are more susceptible to bupivacaine-induced conduction block than are nerve fibers from nonpregnant animals.[124,125] Progesterone administration to nonpregnant rabbits replicates the increased local anesthetic susceptibility of pregnancy. Distention of the lumbar epidural venous plexus during pregnancy may displace the local anesthetic solution to more cranial regions of the spinal canal. Therefore, to prevent excessive cranial spread of anesthesia, a reduced dose of epidural and spinal anesthetics during pregnancy is recommended.

Drug Disposition

Local anesthetics, as the name implies, are deposited at or near the desired site of action. In general, local anesthetics are injected near a nerve bundle. Intraneural injection is painful and may cause nerve damage. The factors that determine the distribution of local anesthetic near the injection site are illustrated in Fig. 14.4. Most clinically used local anesthetics are weak bases and are supplied as mildly acidic hydrochloride salts to improve solubility and stability. In solution, local anesthetics exist as nonionized base (B) and ionized cation (BH^+). The nonionized anesthetic (B) diffuses across the tissue barriers and into the ax-

onal nerve membrane, where membrane stability and neural blockade occur.[1] Nonspecific binding of anesthetic in connective tissue, fat, and muscles and absorption of anesthetic into the vascular and lymph systems reduce the mass (volume × concentration) of the anesthetic available at the neural tissue. Once absorbed into the bloodstream, the local anesthetic is distributed to the lungs, where a significant part (20% to 30%) is absorbed, depending mainly on the physicochemical properties of the local anesthetic.[126,127] After back diffusion of the anesthetic from the lung into the blood, the anesthetic is distributed to systemic tissues (e.g., brain, heart, and liver) and is metabolized in the liver to compounds that are primarily excreted by the kidney and bile.

Absorption

Systemic absorption of local anesthetics is determined primarily by the drug dose (volume or concentration), duration of effect at the site of action, vascularity of the injection site, and use of a vasoconstrictor. Local anesthetic solutions generally are ineffective when applied to the intact skin.

Topical Application Products

Topical application of local anesthetics includes transdermal patches, creams, and iontophoretic delivery systems. Proparacaine is the topical local anesthetic most commonly used in veterinary medicine.

After application of a lidocaine patch (Lidoderm; Endo Laboratories, Chadds Ford, PA), a sufficient amount of 5% lidocaine penetrates the human intact skin to produce analgesia in patients with neuropathic pain associated with postherpetic neuralgia and in patients with postthoracotomy and postmastectomy pain, but less than the amount necessary to produce a complete sensory block.[128] A single patch (10 × 14-cm adhesive bandage) contains 700 mg of lidocaine, which is used in a 12-h-on and 12-h-off period to minimize systemic absorption.

The eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA Cream; Astra Pharmaceuticals, Wilmington, DE) contains 25 mg of lidocaine and 25 mg of prilocaine per each gram or milliliter, which has a sufficiently high concentration of readily available anesthetic base and high water content to penetrate the intact skin and produce reliable cutaneous anesthesia for a wide range of applications in people (e.g., venipuncture in children, radial artery cannulation in adults, and laser treatment)[129,130] and for venipuncture in dogs, cats, rabbits, and rats.[131] In humans, the EMLA preparation is applied as a thick layer under an occlusive dressing, and maximum depth of analgesia of approximately 5 mm is achieved for 30 min after a 90-min application and for a 60-min period after a 120-min application of the cream.[129] In general, the depth of cutaneous analgesia in people ranges from 1 to 6 mm and is believed to be time dependent (1 to 4 h).[132]

Amethocaine cream 1 g (5% wt/wt) applied for 30 or 60 min on the dorsum of the hand produces good analgesia for venous cannulation similar to analgesia produced by 5% EMLA Cream (2.5 g) applied for 30 or 60 min.[133] In comparison to the gel preparation, a 30-min application of the amethocaine-patch system provides profound topical anesthesia of human skin that lasts longer than a 60-min application of EMLA (3 to 6 h vs. 20 min).[134]

ELA-Max Cream (Ferndale Laboratories, Ferndale, MI) is designed to produce analgesia of the skin to reduce venipuncture pain in 20 to 30 min in children without the use of an occlusive dressing. The preparation contains 4% lidocaine, which is liposome encapsulated to enable fast penetration into the stratum corneum. It remains in the epidermis after absorption and minimizes the rapid metabolism of lidocaine.[135] ELA-Max Cream lacks the active ingredient of prilocaine (EMLA Cream), which has been associated with methemoglobinemia in infants.[128,135] ELA-Max Cream may be more suitable for use in cats, which are susceptible to methemoglobin formation.[136]

Numby Stuff patches (Iomed; Salt Lake City, UT), which consist of 2% lidocaine and 1:100,000 epinephrine, are percutaneously administered through iontophoretic drug administration by using a battery generator to deliver small electrical current (4 mA) through two small electrodes.[137,138] Each application device delivers 1 mL of the anesthetic to a depth up to 10 mm in 10 min, giving a transient blanching and tingling of the skin.[138]

Transdermal local anesthesia by iontophoresis, but not EMLA, reduces the pain of intravenous injection of hyperosmolar saline, whereas venipuncture is painless with both methods.[139] The technique involves the use 0.5 mL of lidocaine (2% to 4%) with or without epinephrine 1:50,000 and a current intensity of 0.1 to 0.2 mA/cm^2 at the anode and placement of the cathode on the dorsal surface of the forearm for 10 min.

Although veterinary applications of Lidoderm patches, ELA-Max Cream, Numby Stuff patches, and transdermal local anesthesia by iontophoresis have been minimal, potential uses include local analgesia for small-wound repair, venipuncture, or catheter placement (intravenous and epidural).

Distribution

Local distribution of local anesthetic at the injection site depends on the volume of local anesthetic injected, inclusion of a vasoconstrictor or hyaluronidase in the local anesthetic solution, and the specific drug employed. The specific gravity (baricity) of the solution relative to the specific gravity of the CSF influences distribution within the CNS.

The distribution of amino-ester local anesthetics (e.g., procaine, chloroprocaine, and tetracaine) in body tissues is limited because of their rapid enzymatic hydrolysis by nonspecific plasma pseudocholinesterases. Amide-type local anesthetics (e.g., lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, etidocaine, and ropivacaine) are widely distributed in the body after intravenous bolus injection or a fast rate of vascular absorption. Their pharmacokinetic properties are usually described by a two- or three-compartment model.[140,141]

Plasma Protein Binding

The *plasma protein binding* of local anesthetic drugs refers to the mode by which drugs are transported in the blood. It has a significant effect on numerous aspects of clinical pharmacokinetics and pharmacodynamics.[142] In blood, all amide-linked local anesthetics are partially protein bound, primarily to α_1-acid glycoprotein (AAG) and, to a lesser extent, to albumin[32,141,143] In general, the protein binding of local anesthetics is positively correlated

with the degree of ionization in the physiological pH range and the drug's potency. Plasma protein binding of local anesthetics ranges from 6% for the least potent and short-acting procaine to 95% for the more potent and longer-persisting bupivacaine, etidocaine, and ropivacaine (Table 14.2). Plasma protein binding for articaine and its metabolite articainic acid is between 57% and 90% (average 65%), and the resultant half-lives of the substances are between 1 and 3.9 h.[41]

The free drug concentration in plasma, but not the protein-bound concentration of drug, governs tissue concentrations. The effect of serum protein binding on lidocaine distribution into the brain and CNS in dogs after intravenous lidocaine administration indicates that the free or unbound fraction of lidocaine is an important determinant of lidocaine entry into the brain and CSF.[144] Protein binding of lidocaine in dogs that receive a loading dose (2 mg/kg) and a maintenance infusion (50 μg/kg/h) of lidocaine is associated with increased protein binding and only slight increases of free plasma concentrations of lidocaine.[145]

In dogs, the concentration of lidocaine bound to AAG varies considerably, and it is higher in dogs with inflammatory disease than in healthy dogs.[146] Studies in normal subjects and patients with myocardial infarction, renal disease, hepatic failure, and in patients that are receiving antiepileptic drug therapy, demonstrate a good relationship between the AAG concentration and the binding ratio for lidocaine.[147]

Local anesthetic protein binding approaches saturation only at very high drug concentrations, primarily after prolonged infusion of a long-acting local anesthetic (e.g., ropivacaine or levobupivacaine) and local anesthetic-opioid combination to provide prolonged postoperative analgesia. The slow rise in total plasma concentration with increasing duration of infusion of ropivacaine and levobupivacaine appears to be the predominant reason for rare complications related to systemic toxicity produced by these drugs.[37]

Biotransformation and Excretion

The liver and lungs are major sites for plasma clearance of local anesthetics. Metabolism converts relatively lipid-soluble local anesthetics into smaller, more water-soluble agents.

For esters, the primary step is ester hydrolysis, catalyzed by nonspecific plasma cholinesterases. The rate of plasma hydrolysis is rapid, yielding half-lives measured in seconds, and is inversely related to toxicity (chloroprocaine [most rapid] > procaine > tetracaine [least rapid]).[32,143]

Procaine and benzocaine are metabolized to paraaminobenzoic acid (PABA),[148,149] a breakdown product responsible for allergic reactions and anaphylaxis in some human patients. The majority of the PABA is excreted unchanged or as conjugated product in the urine.[32] Chloroprocaine and tetracaine are metabolized similarly, but not to PABA.

Cocaine is an atypical ester in that it undergoes either ester hydrolysis or *N*-demethylation to norcocaine and then ester hydrolysis and significant hepatic metabolism and urinary excretion. Cocaine is rarely used in veterinary medicine, although it can be abused for stimulation of horses before a race. An intravenous dose of above 0.04 mg/kg increases spontaneous locomotor activity of horses,[150] whereas 200 mg of intravenous cocaine to adult horses undergoing an increased treadmill exercise increased the time to exhaustion by 92 s (15%).[151]

Ester metabolism can, theoretically, be slowed by reduced cholinesterase activity during pregnancy and long-term cholinesterase inhibition via poisons, thereby prolonging the clearance of ester anesthetics and increasing the potential for toxicity.

The amino-amide local anesthetics undergo nearly exclusive metabolism by the liver and hepatic degradation, which requires conjugation with glucuronic acid.[25] Cats glucuronidate drugs to a lesser extent than dogs, making cats more prone to develop toxic side effects when given amide local anesthetics.[25] Little (<5%) of these agents is excreted unchanged in urine.

The order of clearance of amides is prilocaine (most rapid) > etidocaine > lidocaine > mepivacaine or ropivacaine > bupivacaine (least rapid). Lidocaine undergoes oxidative *N*-dealkylation by cytochrome P450IIIA4.[32,143] Mepivacaine, etidocaine, bupivacaine, and ropivacaine also undergo *N*-dealkylation and hydroxylation. They are further conjugated with glucuronide before they are excreted from the body via the urine or bile. Prilocaine undergoes hydrolysis to *o*-toluidine, a compound that can oxidize hemoglobin to methemoglobin.[32,143]

Since all amide local anesthetics are metabolized by the liver, drug clearance is highly dependent on hepatic blood flow, hepatic extraction, and enzyme function. Clearance of amide local anesthetics can be reduced or prolonged by factors that decrease hepatic blood flow, such as β-adrenergic or H_2-receptor blockers, by hypotension during regional and general anesthesia, or by heart or liver failure.[32,143]

Local Anesthetic Toxicity

When careful technique and appropriate dose are used, local anesthetics are relatively free of harmful side effects. However, as with any pharmacological agents, local anesthetics may cause severe toxic reactions after unintentional intravenous administration,[35] vascular absorption of an excessive dose (large volume or high concentration) of the local anesthetic agent,[152] or ingestion of topical local anesthetic preparations.[153]

Doses of local anesthetics, especially those for cats and small dogs, should always be carefully calculated and reduced in sick animals. For example, in healthy dogs and cats, the dose of lidocaine should not exceed 12 and 6 mg/kg, respectively, to prevent toxicity. Repeated applications, the application of higher than the recommended doses, or impaired elimination may all contribute to increasing blood concentration of local anesthetics. Potential damage may also occur from chemical contamination of the local anesthetic solution, allergic reactions, or methemoglobinemia, or from neural ischemia produced by local pressure or hypotension. The systemic toxicity of local anesthetics involves primarily alterations in the CNS and the cardiovascular system.

Central Nervous System Toxicity

In general, toxic and lethal doses of local anesthetic drugs produce signs of CNS excitation leading ultimately to convulsive activity followed by CNS depression (unconsciousness and coma)

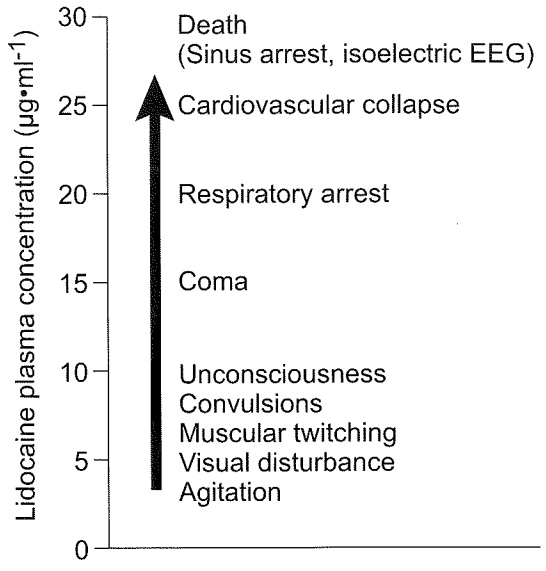


Fig. 14.5. Toxic effects produced by increasing lidocaine plasma concentrations. EEG, electroencephalogram.

with eventual respiratory arrest and cardiovascular collapse.[10] Acute CNS toxicity occurs at lower doses than those required to produce acute cardiovascular system toxicity.

As the plasma concentration of the drug increases, humans experience a predictable sequence of signs and symptoms, such as numbness of tongue, light-headedness, visual disturbance, muscle twitching, unconsciousness, and convulsions, which may progress to coma, respiratory arrest, cardiovascular depression, and death (Fig. 14.5). The seizure frequency and accompanying cardiovascular changes in patients undergoing various regional block techniques (e.g., brachial plexus block or epidural and caudal regional anesthesia) have been reviewed, indicating a rate of seizure development with caudal > brachial > epidural anesthetics and no adverse cardiovascular, pulmonary, or nervous system events occurring with seizures.[154]

In small animals, low concentrations of local anesthetics produce sedation, whereas higher concentrations produce seizures, probably because of selective depression of inhibitory fibers in the subcortical area (amygdala), with subsequent spread, leading to grand mal seizures. Muscle twitching and convulsions are usually the first signs of local anesthetic toxicity observed in dogs and cats. More potent local anesthetics consistently produce seizures at lower blood concentrations and lower doses than do the less potent local anesthetics.

In awake dogs, the mean cumulative dose of serially and rapidly administered intravenous local anesthetics to produce convulsions is 4.0 mg/kg tetracaine, 5.0 mg/kg bupivacaine, 8.0 mg/kg etidocaine, and 22 mg/kg lidocaine, indicating a relative CNS toxicity of tetracaine, bupivacaine, etidocaine, and lidocaine of about 1:1.2:2:4.[81]

In cats, procaine (the least potent CNS depressant, less lipid soluble and less protein bound) produces seizures at 35 mg/kg intravenously (IV), whereas bupivacaine (one of the most potent CNS depressants, highly lipid soluble and highly protein bound) induces convulsions at approximately 5 mg/kg IV.[155,156] Intravenously administered lidocaine at a dose of 11.7 ± 4.6 mg/kg causes seizures in cats.[157] Increased arterial PCO_2 (68 to 81 mm Hg) and decreased pH reportedly decrease the convulsive dose of procaine, lidocaine, and bupivacaine by approximately 50% in cats.[155]

Horses are reported to be more sensitive to the CNS toxicity of lidocaine than other species, although the mechanism of this increased sensitivity is not known. Seizures in horses may occur at plasma levels of 600 ng of procaine/mL[158] and 6.0 μg of lidocaine/mL,[159] respectively, and usually are brief because of rapid redistribution. Such concentrations are not readily achieved with careful local and regional anesthetic techniques; for example, the procaine plasma concentration can reach 400 ng/mL within 1 h after subcutaneous injection of 3.3 mg of procaine/kg of horse body weight, whereas the lidocaine plasma concentration approaches 3.5 μg/mL approximately 15 min after a flank "line block" using 10 mg of lidocaine/kg of body weight.

The toxic effects of local anesthetics within the CNS are enhanced by increased cerebral blood flow, by increased concentration of ionized drug in the brain, or by the direct excitatory effect on subcortical structures.

Cardiovascular Toxicity

Since an alarming editorial in 1979 about cardiac arrest in humans following regional anesthesia with etidocaine and bupivacaine,[160] ropivacaine and, recently, levobupivacaine were developed as alternative long-acting amide local anesthetics with less potential for cardiovascular toxicity.[161–166]

Local anesthetic cardiovascular toxicity may result from direct electrophysiological and mechanical effects on the heart or the peripheral circulation and from local anesthetic actions on the autonomic nervous system. The use of lower concentrations can result in CNS excitation, with increased heart rate, arterial blood pressure, pulmonary artery pressure, and cardiac output. With larger toxic blood concentrations, the systemic effects are characterized by decreased heart rate, arterial blood pressure, pulmonary artery pressure, and cardiac output.[167,168]

Results from animal studies demonstrate increased systemic toxicity associated with bupivacaine and etidocaine as compared with lidocaine, the most extreme of which include severe CNS and cardiovascular reactions, eventually leading to hemodynamic instability, cardiovascular collapse, and death. In intact, ventilated dogs anesthetized with pentobarbital, minimal changes in various cardiovascular functions are seen with lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine at doses of 0.3 to 3 mg/kg. At 10 mg/kg, lidocaine, mepivacaine, and prilocaine produce moderate hypotension and increased pulmonary vascular resistance, and bupivacaine and etidocaine produce significant decreases in cardiac output and stroke volume.[81] Irreversible cardiovascular depression is not produced with lidocaine, bupivacaine, etidocaine, or tetracaine in ventilated dogs anesthetized with pentobarbital, until the blood concentration is at least 3.5 to 6.7 times the dose producing seizures.[81] However, in humans and animals, both bupivacaine and etidocaine administration have

produced simultaneous CNS and cardiovascular toxicity manifested as severe cardiac dysrhythmia, fibrillation, and cardiac arrest.[32,160,168,169]

In another study of pentobarbital-anesthetized dogs, the intravenous administration of bupivacaine (4 mg/kg) or etidocaine (8 mg/kg) depressed electrophysiological and hemodynamic function; lidocaine (16 mg/kg) induced bradycardia and arterial hypotension, whereas mepivacaine (12 mg/kg) induced minimal cardiovascular changes.[170] The cumulative lethal dose varies from approximately 80 mg/kg for lidocaine and mepivacaine to 40 mg/kg for etidocaine and 20 mg/kg for bupivacaine in ventilated dogs anesthetized with pentobarbital.[171] Direct injection of equipotent doses of 2% lidocaine (8 mg) or 0.5% bupivacaine (2 mg) in a 4:1 ratio into a branch of the left coronary artery in morphine (2.5 mg/kg subcutaneously) + α-chloralose (10 mg/kg/h IV)–anesthetized and ventilated dogs produced a 50% reduction of systolic contraction that lasted 25% longer after bupivacaine than after lidocaine injection.[172]

When a comparable prolongation of the QRS interval (as a measure of electrophysiological toxicity) was recorded in pentobarbital-anesthetized pigs after injection of 2 mg of bupivacaine, 4.5 mg of ropivacaine, or 30 mg of lidocaine into the left anterior descending coronary artery, the electrophysiological toxicity ratio for bupivacaine-ropivacaine-lidocaine was 15:6.7:1.[173] Thus, ropivacaine appears to provide a much greater margin of safety than does bupivacaine.

In sheep, the mean fatal dose of intravenous lidocaine is 30.8 ± 5.8 mg/kg, that of bupivacaine is 3.7 ± 1.1 mg/kg, and that of ropivacaine is 7.3 ± 1.0 mg/kg; thus the ratio of fatal doses of lidocaine, bupivacaine, and ropivacaine is approximately 9:1:2.[174] Respiratory depression with bradycardia and hypotension without arrhythmias were the causes of death in lidocaine-treated sheep, whereas most bupivacaine-treated or ropivacaine-treated sheep died after sudden onset of ventricular tachycardia and fibrillation. Not surprisingly, the cardiotoxicity of lidocaine and bupivacaine in awake, unanesthetized sheep is enhanced by hypercarbia, acidosis, and hypoxia.[175]

Local anesthetics bind and inhibit cardiac sodium channels.[168,176] Bupivacaine binds more readily and for a longer duration to cardiac sodium channels than does lidocaine.[177] The bupivacaine $S-(-)$ isomer binds cardiac sodium channels less readily than does the $R-(+)$ isomer, forming the basis for the development of levobupivacaine and ropivacaine.[37] In vitro studies of guinea pig hearts (Langendorff model) indicate that $R-(+)$ bupivacaine, based on intracardiac distribution, prolongs atrioventricular (AV) conduction more and produces more second-degree AV conduction blocks than does $S-(-)$ or racemic bupivacaine.[178] Similarly, $S-(-)$ bupivacaine produces less QRS widening and fewer AV conduction blocks, less ventricular fibrillation, and less asystole in paced rabbit hearts than does $R-(+)$ or racemic bupivacaine.[179] Comparative effects of equal concentrations of bupivacaine, levobupivacaine, and ropivacaine in electrically paced rabbit hearts (210 beats/min) indicate that the free concentration of the three drugs necessary to double the basal QRS duration is 2.4, 7.2, and 14.4 μg/mL for race-mic bupivacaine, levobupivacaine, and ropivacaine, respectively.[180]

Toxicosis After Ingestion or Application of Topical Preparations

Topical local anesthetic preparations containing lidocaine, benzocaine, tetracaine, and dibucaine, which are in many prescription and nonprescription products, such as ointments, teething gels, suppositories, and aerosols, can be hazardous to animals if ingested. Ingestion of topical benzocaine preparations or spray before endotracheal intubation has produced varying degrees of vomiting, cyanosis, dyspnea, respiratory depression, prolonged sedation, hypotension, cardiac arrhythmias, tremors, seizures, and death in dogs and cats. Likewise, digestion of ointments and creams containing 0.5% and 1.0% dibucaine hydrochloride, which may not be considered dangerous by pet owners, has produced salivation, vomiting, hypothermia, bradycardia, hypotension, weakness, seizures, dysrhythmia, and death in dogs and cats. Between 1995 and 1999 the National Animal Poison Control Center (NAPCC) recorded over 70 cases of toxicosis induced by either ingestion or the inappropriate use of lidocaine, benzocaine, or dibucaine in a variety of animals, including dogs, cats, and ferrets. The clinical signs in a variety of animal species, including dogs, cats, and ferrets, with lidocaine and dibucaine toxicosis included salivation, vomiting, hypothermia, depression, tremors, weakness, bradycardia, hypotension, and seizures.[153]

Local Toxicity

Neurotoxicity

When properly used, local anesthetics rarely produce neurotoxic effects or localized tissue damage. Neurotoxicity of local anesthetics can be demonstrated in vitro by the collapse of growth cones and neuritis in cultured neurons.[181] Comparison of seven local anesthetics in a study on growing neurons of the freshwater snail demonstrates neurotoxicity in this order: procaine = mepivacaine (least neurotoxic) < ropivacaine = bupivacaine < lidocaine < tetracaine < dibucaine (most neurotoxic). Similarly, mepivacaine also induced less growth cone collapse and neurite degeneration in the growing dorsal root ganglion neurons from chick embryos than did lidocaine, bupivacaine, or ropivacaine, indicating that mepivacaine is the safest among clinically used local anesthetics.[182]

During the 1980s, 2-chloroprocaine (Nesacaine) occasionally produced cauda equina syndrome in people when large doses (formulated with the antioxidant sodium metabisulfite at an acidic pH) were accidentally injected into the subarachnoid space.[32,183–185] Experiments with sheep and monkeys document that a large volume (10 mL) of subarachnoid administration of 2-chloroprocaine (3%), bupivacaine (0.75%), or the carrier solution of 2-chloroprocaine (Nesacaine) is neurotoxic and that no local anesthetic appears to be more toxic than another when injected in large volumes into the subarachnoid space of sheep and monkeys.[186] The large doses and volumes of local anesthetics simulate the clinical reality of accidental spinal anesthesia when epidural anesthesia is intended.

Several studies have been completed since then to evaluate the potential neurotoxicity of repeated injections or continuous infusions of local anesthetics in laboratory animals in situ and vitro. Experiments using surgically exposed vagus nerves in rabbits bathed in situ for up to 1 h in 1.5% 2-chloroprocaine, 2% lidocaine, or 0.75% bupivacaine indicate that 2-chloroprocaine is more neurotoxic than either lidocaine or bupivacaine.[187] Histological sections of nerves excised 10 to 12 days after drug exposure revealed epineurial cellular infiltration and fibrosis, perineurial fibrosis, and axonal degeneration following the administration of 2-chloroprocaine or a mixture of 2-chloroprocaine and bupivacaine, and only minor pathology following exposure to lidocaine or bupivacaine.

Controversy exists about whether lidocaine produces persisting sacral deficits and whether it may be associated with an excessive incidence of transient radicular irritation after spinal anesthesia in humans.[188] Solutions of 5% lidocaine and 0.5% tetracaine, unlike other spinal local anesthetic solutions (1.5% lidocaine with or without 7.5% dextrose, or 0.75% bupivacaine without dextrose), have been associated with clinical cases of cauda equina syndrome after continuous spinal anesthesia. These solutions cause irreversible conduction block in desheathed amphibian nerves 15 min after exposure to 5% lidocaine or 0.5% tetracaine.[189] Neurotoxic effects, including paralysis, have been produced after subarachnoid infusion of 100 μL/h of 1.5% lidocaine, 0.5% bupivacaine, or 2% 2-chloroprocaine in rats. The incidence of paralysis depended on the duration of exposure to the local anesthetic and was more intense in rats receiving lidocaine or 2-chloroprocaine than those infused with bupivacaine.[190]

Myotoxicity

All clinically used local anesthetics are myotoxic, with a drug-specific and dose-dependent rate of toxicity that worsens with serial or continuous administration.[191] Some reports indicate that single and repeated injections of clinical doses of mepivacaine (Carbocaine)[192] or bupivacaine (Marcaine)[193] produce skeletal muscle damage in rats. With 200 μL of local anesthetic (1% procaine, 0.2% tetracaine, 0.5% lidocaine, 0.75% bupivacaine, 2% chloroprocaine, 0.25% dibucaine, and 0.5% lidocaine with 1:200,000 epinephrine, and 2% piperocaine) injected into the tibialis anterior muscle of rats, the muscle fibers recovered from the initial damage in 30 days, with relatively few long-term residual effects.[194]

The administration of 20 mL of bupivacaine (5 mg/mL) or ropivacaine (7.5 mg/mL) via catheter to the femoral nerve of minipigs, and subsequent continuous infusion of bupivacaine (2.5 mg/mL) or ropivacaine (3.75 mg/mL) over 6 h, induced necrosis and apoptosis in muscle fibers with bupivacaine and less severe fiber injury with ropivacaine, without affecting vasculature, neural structures, and connective tissues.[195] The administration of bupivacaine and ropivacaine induces Ca^{2+} release of the sarcoplasmic reticulum and simultaneously inhibits Ca^{2+} reuptake into the sarcoplasmic reticulum, suggesting that these synergistic effects may be an important mechanism in bupivacaine and ropivacaine's observed myotoxicity.[195]

Although skeletal muscle damage from local anesthetics is not a major clinical problem, case reports have been published of local anesthetic-induced myotoxicity in humans after local and regional anesthesia, peripheral nerve blocks, retrobulbar injections, and trigger-point infiltration for treatment of myofascial pain.[191]

Methemoglobinemia

Methemoglobinemia (MHG) or increased concentration of methemoglobin (MHb) in the blood is defined as an altered state of hemoglobin whereby the ferrous form of iron (Fe^{2+}) is oxidized to the ferric state (Fe^{3+}), which increases oxygen affinity for hemoglobin (as seen with MHG) and reduces oxygen release at tissues.[196] In addition, oxidative denaturation of hemoglobin can cause Heinz-body formation, which can lead to erythrocyte lysis. MHG can cause hypoxia, cyanosis, or even death.

A number of local anesthetic agents, most notably benzocaine and prilocaine, and less often procaine and lidocaine, are implicated as causative agents. Benzocaine induces MHG in several species, whereas lidocaine may increase MHG in cats and people.[197] It appears that these agents do not directly produce MHG, but rather that one of their metabolites, i.e., *o*-toluidine, is responsible.

An intense chocolate brown–colored blood and central cyanosis unresponsive to the administration of 100% oxygen suggest the diagnosis of MHG. MHb concentrations of 15% or more cause a brown discoloration to the blood, which is visible on a white paper towel. Laboratory confirmation is by blood cooximetry, indicating an MHb concentration of greater than 15% (1% to 2% is normal). Spectrophotometry for quantitating the percentage of MHb may be available in a local human hospital laboratory. Blood smears can be useful in determining the presence and degree of Heinz-body formation.

The clinical consequences of MHG are related to the blood concentration of MHb. In humans, dyspnea, nausea, and tachycardia occur at an MHb concentration of > 30%, whereas lethargy, stupor, and deteriorating consciousness occur as the MHb concentration approaches 55%.[198] Acquired toxic MHG has been induced with benzocaine topical anesthetics (spray, cream, and ointment), which were used for bronchoscopic procedures,[199] transesophageal echocardiography,[200] fiberoptic orotracheal intubation, and skin application.[201] Peak MHb concentrations were directly related to the total dose of benzocaine or prilocaine administered and did not occur until 4 to 8 h after epidural administration of prilocaine.[202]

MHG has been induced by the nasal, oropharyngeal, and dermal applications of benzocaine in sheep,[203] dogs, and cats.[204–206] A 2-s spray of benzocaine (estimated dose, 56 mg) to the mucous membranes of the nasopharynx of dogs, cats, monkeys, rabbits, and miniature pigs produces MHb concentrations, ranging from 3.5% to 38%, 15 to 60 min after drug administration.[191] A 2-s benzocaine dose and a 10-s dose produce MHb up to 26.4 and 50.5%, respectively, in sheep.[197]

Benzocaine is combined with butamben and tetracaine in a topical anesthetic spray (Cetacaine) that has been commonly

used to desensitize the larynx before intubation.[201] Cats are well recognized to be at an increased risk for developing MHG and Heinz-body anemia with benzocaine-containing products, including Cetacaine. Because of the susceptibility of cats, ferrets, or other exotic animals to MHG, the topical use of Cetacaine should be avoided in these species.

Allergic Reactions

Although allergic reactions to local anesthetics may occur, they are uncommon and often misdiagnosed after accidental intravenous injection of local anesthetics. True anaphylaxis or life-threatening allergic immune reaction is mediated by immunospecific antibodies (immunoglobulins E or G) that interact with mast cells, basophils, or the complement system to liberate vasoactive mediators and recruit other inflammatory cells. Such reactions have been documented with amino-ester local anesthetics (e.g., procaine), particularly those that are metabolized directly to PABA, which is a common allergen. Anaphylaxis to amide local anesthetics (e.g., lidocaine) is much less common.[207] Some reaction may result from hypersensitivity to a preservative (e.g., methylparaben, whose chemical structure is similar to that of PABA). Allergic reactions of dogs and cats treated with amide-linked local anesthetics are very rare, which is probably because of their different metabolism and breakdown products when compared with humans.

Adverse drug reactions may mimic anaphylaxis, characterized by bronchospasm, upper-airway edema, vasodilatation, increased capillary permeability, and cutaneous wheal and flare. Rapid cardiopulmonary intervention with airway maintenance, epinephrine administration, and volume expansion is essential to avoid a fatal outcome. Patients with local anesthetic allergy can have their skin tested to determine nonreactive agents.

Treatment of Adverse Reactions

Treatment of adverse reactions after administration of local anesthetics depends on an animal's presenting signs, and involves stabilizing, decontaminating, and supporting the patient.

When local anesthetic-induced convulsions occur, hypoxia, hypercarbia, and acidosis develop rapidly.[208] Because these metabolic changes greatly increase the toxicity of local anesthetics,[175,209,210] prompt therapy with oxygen administration by mask to a dyspneic patient and supporting ventilation (e.g., endotracheal intubation, oxygen supplementation, and positive-pressure ventilation) is indicated.[211]

The administration of oxygen by mask and intravenous fluids are often all that is necessary to treat mild signs of local anesthetic toxicity, including mild seizures.[212] Anticonvulsant drug therapy is indicated if seizure activity interferes with ventilation or is prolonged. Diazepam or midazolam can be given intravenously in dogs and cats at 0.5 to 1 mg/kg in increments of 5 to 10 mg to effect, with minimal side effects. Thiopental or propofol (1 to 2 mg/kg IV) acts more rapidly but may produce greater cardiorespiratory depression than that produced with benzodiazepine therapy.[213,214]

Acute hypotension may be treated with intravenous fluids (10 mL/kg/h) and vasopressors (phenylephrine, 0.5 to 5.0 μg/kg/min, or norepinephrine, 0.02 to 0.2 μg/kg/min). Hemoglobin-based oxygen carriers (HBOCs), such as HBOC 301 (Oxyglobin) or HBOC 201 (Hemopure and Biopure) (Biopure, Cambridge, MA), are polymerized bovine hemoglobin glutamers that provide a most effective colloid, similar to plasma, and oxygen-carrying effect.[215,216] Oxyglobin can be a good substitute for stored blood, which may not always be available. Severely hypotensive dogs and cats with obvious severe blood loss (>30 mL/kg in dogs, 15 mL/kg in cats) and those that continue to be dyspneic despite oxygen therapy may rapidly improve from an initial Oxyglobin bolus (4 to 6 mL/kg in dogs, and 2 to 3 mL/kg in cats) as a stopgap measure to prevent cardiovascular collapse. A one-time intravenous dose of 30 mL/kg Oxyglobin at a rate of 10 mL/kg/h may be given to hypotensive dogs to increase arterial pressure and flow. Every 10 mL of Oxyglobin infused contains 1.3 g of HBOC. Caution must be exercised to avoid intravascular volume overload, which can produce pulmonary edema, pleural effusion, mucous membrane discoloration, pigmenturia, vomiting, and neurological abnormalities, particularly in small dogs and cats.[215]

An intravenous bolus of epinephrine (1 to 15 μg/kg) may be required in presence of myocardial failure. Guidelines for cardiopulmonary resuscitation should be followed when toxicity progresses to cardiac arrest. Animal studies suggest that lidocaine intoxication causes myocardial depression that can be successfully treated with continued advanced cardiac life support.[217] In contrast, cardiotoxic effects in anesthetized dogs associated with incremental overdosage of bupivacaine, levobupivacaine, or ropivacaine are not as easily treated by resuscitation efforts. The administration of epinephrine may lead to severe arrhythmias, including ventricular fibrillation, with a subsequent mortality rate from bupivacaine, levobupivacaine, ropivacaine, and lidocaine of approximately 50%, 30%, 10%, and 0%, respectively.[217]

Even though the risk of cardiovascular toxicity of ropivacaine has not been completely eliminated, ropivacaine may offer clear advantages over bupivacaine, in that ropivacaine accumulates less sodium-channel blockade at physiological heart rates, dissociates from sodium channels more rapidly, is less cardiotoxic, and is more susceptible to treatment than is bupivacaine.[218,219]

Ventricular dysrhythmias, including life-threatening ventricular tachycardia associated with local anesthetic toxicity in dogs, have been treated with bretylium tosylate (2 to 6 mg/kg IV).[220,221] Procainamide and quinidine may be effective treatments for ventricular antiarrhythmias in dogs and cats. Lidocaine is generally contraindicated in patients with amide local anesthetic toxicity.

MHG is easily treated and rapidly reduced to hemoglobin by slow (over several minutes) intravenous administration of a 1% solution of methylene blue (methylthioninium chloride, 4 mg/kg in dogs and 1 to 2 mg/kg in cats).[198] The dose can be repeated in dogs, but repeated administration of methylene blue in cats is controversial because of the risk of Heinz-body anemia and the aggravation of subsequent hemolysis without further lowering MHb content.[222]

Tachyphylaxis

Tachyphylaxis, or the acute tolerance to local anesthetic agents, is defined as decreases in intensity, segmental spread, or duration after repeated administration of equal doses of an anesthetic. Various ester-amide–type local anesthetics (e.g., cocaine, procaine, and tetracaine) and amide-type local anesthetics (e.g., lidocaine, lidocaine–carbon dioxide, mepivacaine, bupivacaine, etidocaine, and dibucaine) have been used at increasing doses to maintain a similar level of effect during surface anesthesia, nerve blocks, brachial plexus block, and epidural and subarachnoid anesthesia. The underlying mechanisms of tachyphylaxis are not well understood. Local alterations in disposition and absorption of local anesthetics—but not in structure (ester vs. amide) or the pharmacological properties of local anesthetics themselves (e.g., brief vs. long acting), technique, mode of administration (intermittent vs. continuous), and pharmacodynamic processes (interactions at receptor sites)—may all play a role in the development of tachyphylaxis.[223]

Choices of Local Anesthetics

The use of specific local anesthetics for local and regional anesthetic and analgesic techniques in animals is described in Chapters 20 (dogs), 21 (cats), 22 (horses), and 23 (cattle, sheep, goats, and pigs).

Local Anesthetics Approved for Veterinary Use by *Codified Federal Register* (*CFR*)

Lidocaine injection with epinephrine: cats, cattle, dogs, and horses (21 *CFR* 522.1244, p. 280, April 1, 1993, editions).

Mepivacaine hydrochloride injection: horses (21 *CFR* 522.1372, p. 281, April 1, 1993, editions).

Proparacaine hydrochloride ophthalmic solution: animal species not specified (21 *CFR* 524.1883, p. 338, April 1, 1993, editions).

The *CFR* also lists a number of combination products containing local anesthetics plus corticosteroid or antimicrobial agents for treatment of surface bacterial infections and/or allergy.

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