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with 441 illustrations

978-0-323-07413-1

3251 Riverport Lane

St. Louis, Missouri 63043

Handbook of Local Anesthesia

ISBN: 978-0-323-07413-1

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Library of Congress Cataloging-in-Publication Data

Malamed, Stanley F., 1944-

Handbook of local anesthesia / Stanley F. Malamed.—6th ed.

p. ; cm.

Includes bibliographical references and index.


I. Title.


617.9'67–dc23

2011051243

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Printed in China
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To Beverly, Heather, Jennifer, and Jeremy, and the next generation: Matthew, Rachel, Gabriella, Ashley, Rebecca, Elijah, and Ethan

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Preface

The sixth edition of Handbook of Local Anesthesia!

As happened with previous editions, I truly find it hard to comprehend how many years have transpired since the 1st edition was published in 1978. It has been 8 years since the fifth edition and in this time there have been a significant number of changes, many of them advances, in the art and science of pain control in dentistry.

Though the drugs remain the same—articaine HCl, bupivacaine HCl, lidocaine HCl, mepivacaine HCl, and prilocaine HCl—the years since the fifth edition have seen the introduction and refinement of drugs and devices which work to help the dental profession come ever closer to the twin goals of truly pain free dentistry and truly pain free local anesthetic injections.

As I have stated repeatedly in previous editions, “Local anesthetics are the safest and the most effective drugs available in all of medicine for the prevention and the management of pain. Indeed, there are no other drugs that truly prevent pain; no other drugs which actually prevent a propagated nociceptive nerve impulse from reaching the patient's brain, where it would be interpreted as pain. Deposit a local anesthetic drug in close proximity to a sensory nerve and clinically adequate pain control will result in essentially all clinical situations.”

Find the nerve with a local anesthetic drug and pain control is virtually assured. Yet in certain clinical situations “finding the nerve” remains a vexing problem. This is especially so in the mandible, primarily
permanent mandibular molars. Over my 39 years as a teacher of anesthesia in dentistry I and my dentist anesthesiologist colleagues have worked at “fixing” this problem.

Have we succeeded? Not yet.

Are we getting close to a solution? Yes.

This sixth edition of Local Anesthesia includes new and/or expanded discussions of the periodontal ligament (PDL) injection—including the use of computer-controlled local anesthetic delivery (C-CLAD) systems for PDL (and other injections); the administration of the local anesthetic articaine HCl by mandibular infiltration in the adult mandible; buffering of local anesthetic solutions (the local anesthetic “ON” switch) to increase patient comfort during injection, decrease onset time of anesthesia, and, perhaps, increase the depth of anesthesia; phentolamine mesylate (the local anesthetic “OFF” switch) giving the doctor the opportunity to significantly minimize the duration of a patients residual soft tissue anesthesia, thereby minimizing the risk of self-inflicted soft tissue injury.

I have asked Dr. Mark Hochman to rewrite the discussions in this edition on C-CLAD devices (Chapter 5—The Syringe) and the local anesthetic techniques associated with it (Chapter 15—Supplemental Injections and Chapter 20—Future Considerations). Dr. Hochman has been intimately involved with the development of C-CLAD since the mid-1990s and is the author of a number of refereed papers on the subject including two injection techniques—AMSA (anterior middle superior alveolar nerve block) and P-ASA (palatal—anterterior superior alveolar nerve block) that were developed as a result of his research into computer delivery of local anesthetics.

A DVD accompanied the fifth edition of Local Anesthesia. It followed the structure of the textbook, providing clinical demonstrations of the techniques and concepts presented in the text. The DVD has proven to be a highly effective teaching device and is used, both legally and (sadly) illegally, by students, dentists and dental hygienists throughout the world.

A supplemental disk has been incuded with the original 2-disk set which accompanies this sixth edition. The disk presents clinical updates on a number of the newer additions to the local anesthetic armamentarium. It is my feeling, as an educator that the combination of the written text plus the visual impact of the DVD provides a more optimal learning experience for all who come to study this critically important subject.

Feedback from readers of this textbook is always appreciated. Should errors be noted, or suggestions for improvement be made, contact me at malamed@usc.edu.

Stanley F. Malamed
October 2011
Los Angeles, California, USA

Acknowledgments

The people involved with the video production of the new supplemental DVD cannot receive enough thanks: Dr. Joseph Massad and his excellent team at Millennium Productions.
Thanks, too, to the manufacturers of local anesthetic drugs and devices in North America, including Beutlich Pharmaceuticals; Dentsply; Kodak (Cook-Waite); Midwest; Milestone Scientific; Novocol; Septodont, Inc; and Sultan Safety, LLC, for their assistance in supplying photographs and graphics for use in this edition.

I also want to thank Brian S. Loehr, Senior Content Development Specialist; Rachel E. McMullen, Senior Project Manager; and John J. Dolan, Executive Content Strategist, from Mosby (an affiliate of Elsevier) who had the unenviable task of dealing with a frequently lazy, usually hard-to-reach author. Their perseverance—once again—has paid off with this sixth edition.

Finally, I wish to thank the many members of our profession, the dentists and dental hygienists, who have provided me with written and verbal input regarding prior editions of this textbook. Many of their suggestions for additions, deletions, and corrections have been incorporated into this new text. Thanks to you all!

Stanley F. Malamed

December 2011

Los Angeles, California

New to this Edition

DVD Supplement

A supplemental disk has been added to the original 2-disk set. The new DVD supplement presents clinical updates on a number of the newer additions to the local anesthetic armamentarium, including the local anesthesia “ON” and “OFF” switches, and Computer-Controlled Local Anesthetic Delivery (C-CLAD).
New Information

Updated discussions of the armamentarium needed to succeed in local anesthesia delivery
Computer-controlled local anesthetic delivery (C-CLAD) systems
Handbook of Local Anesthesia, 6th Edition
New Illustrations Identify Clinically Important Anatomy
Part I The Drugs

The Drugs

Chapter 1 Neurophysiology

Chapter 2 Pharmacology of Local Anesthetics

Chapter 3 Pharmacology of Vasoconstrictors

Chapter 4 Clinical Action of Specific Agents
The Drugs

In the first section of this book, the pharmacologic and clinical properties of the classes of drugs known as local anesthetics (Chapter 2) and vasoconstrictors (Chapter 3) are discussed. Knowledge of both the pharmacologic and clinical properties of these drugs, by all persons permitted to administer them, is absolutely essential for their safe use and for a better understanding of those potentially life-threatening systemic reactions associated with their administration. Emphasis is placed on local anesthetic drug combinations currently used in anesthesia in dentistry in North America (Chapter 4).

Chapter 1 provides a background for understanding how local anesthetics work to transiently block nerve conduction, thus preventing pain from being experienced. The anatomy and physiology of normal neurons and nerve conduction are reviewed as a background for the discussion, which, in subsequent chapters, takes up the pharmacology and clinical actions of various specific agents.
Chapter 1 Neurophysiology

Desirable Properties of Local Anesthetics

Local anesthesia has been defined as loss of sensation in a circumscribed area of the body caused by depression of excitation in nerve endings or inhibition of the conduction process in peripheral nerves. An important feature of local anesthesia is that it produces this loss of sensation without inducing loss of consciousness. In this one major area, local anesthesia differs dramatically from general anesthesia.

Many methods are used to induce local anesthesia:

1. Mechanical trauma (compression of tissues)
2. Low temperature
3. Anoxia
4. Chemical irritants
5. Neurolytic agents such as alcohol and phenol
6. Chemical agents such as local anesthetics

However, only those methods or substances that induce a transient and completely reversible state of anesthesia have application in clinical practice. Following are those properties deemed most desirable for a local anesthetic:

1. It should not be irritating to the tissue to which it is applied.
2. It should not cause any permanent alteration of nerve structure.
3. Its systemic toxicity should be low.
4. It must be effective regardless of whether it is injected into the tissue or is applied locally to mucous membranes.
5. The time of onset of anesthesia should be as short as possible.
6. The duration of action must be long enough to permit completion of the procedure yet not so long as to require an extended recovery.

Most local anesthetics discussed in this section meet the first two criteria: They are (relatively) nonirritating to tissues and are completely reversible. Of paramount importance is systemic toxicity, because all injectable and most topical local anesthetics are eventually absorbed from their site of administration into the cardiovascular system. The potential toxicity of a drug is an important factor in its consideration for use as a local anesthetic. Toxicity varies greatly among the local anesthetics currently in use. Toxicity is discussed more thoroughly in Chapter 2. Although it is a desirable characteristic, not all local anesthetics in clinical use today meet the criterion of being effective, regardless of whether the drug is injected or applied topically.
Several of the more potent injectable local anesthetics (e.g., procaine, mepivacaine) prove to be relatively ineffective when applied topically to mucous membranes. To be effective as topical anesthetics, these drugs must be applied in concentrations that prove to be locally irritating to tissues while increasing the risk of systemic toxicity. Dyclonine, a potent topical anesthetic, is not administered by injection because of its tissue-irritating properties. Lidocaine and tetracaine, on the other hand, are effective anesthetics when administered by injection or topical application in clinically acceptable concentrations. The last factors—rapid onset of action and adequate duration of clinical action—are met satisfactorily by most of the clinically effective local anesthetics in use today. Clinical duration of action does vary considerably among drugs and also among different preparations of the same drug, as well as by the type of injection administered (e.g., nerve block vs. supraperiosteal). The duration of anesthesia necessary to complete a procedure is a major consideration in the selection of a local anesthetic.

In addition to these qualities, Bennett lists other desirable properties of an ideal local anesthetic:

1. It should have potency sufficient to give complete anesthesia without the use of harmful concentrated solutions.
2. It should be relatively free from producing allergic reactions.
3. It should be stable in solution and should readily undergo biotransformation in the body.
4. It should be sterile or capable of being sterilized by heat without deterioration.

No local anesthetic in use today satisfies all of these criteria; however, all anesthetics do meet a majority of them. Research is continuing in an effort to produce newer drugs that possess a maximum of desirable factors and a minimum of negative ones.

**Fundamentals of Impulse Generation and Transmission**

The discovery in the late 1800s of a group of chemicals with the ability to prevent pain without inducing loss of consciousness was one of the major steps in the advancement of the medical and dental professions. For the first time, medical and dental procedures, could be carried out easily and in the absence of pain, a fact that is virtually taken for granted by contemporary medical and dental professionals and their patients.

The concept behind the actions of local anesthetics is simple: They prevent both the generation and the conduction of a nerve impulse. In effect, local anesthetics set up a chemical roadblock between the source of the impulse (e.g., the scalpel incision in soft tissues) and the brain. Therefore the aborted impulse, prevented from reaching the brain, cannot be interpreted by the patient as pain.

This is similar to the effect of lighting the fuse on a stick of dynamite. The fuse is the “nerve,” whereas the dynamite is the “brain.” If the fuse is lit and the flame reaches the dynamite, an explosion occurs (Fig. 1-1). When a nerve is stimulated, an impulse is propagated that will be interpreted as pain when it reaches the brain. If the fuse is lit, but “water” (e.g., local anesthetic) is placed somewhere between the end of the fuse and the dynamite stick, the fuse will burn up to the point of water application and then die out. The dynamite does not explode. When a local anesthetic is placed at some point between the pain stimulus (e.g., the drill) and the brain, the nerve impulse is still propagated and travels up to the point of local anesthetic application and then
Figure 1-1 The fuse is lit and the flame reaches the dynamite; an explosion occurs, and the patient experiences pain.

OW!!!

“dies,” never reaching the brain, and pain does not occur (Fig. 1-2).

How, in fact, do local anesthetics, the most used drugs in dentistry, function to abolish or prevent pain? Following is a discussion of current theories seeking to explain the mode of action of local anesthetic drugs.
To understand their action better, however, the reader must have an acquaintance with the fundamentals of nerve conduction. A review of the relevant characteristics and properties of nerve anatomy and physiology follows.

**The Neuron**

The neuron, or nerve cell, is the structural unit of the nervous system. It is able to transmit messages between the central nervous system (CNS) and all parts of the body. There are two basic types of neuron: sensory (afferent) and motor (efferent). The basic structure of these two neuronal types differs significantly (Fig. 1-3).

Sensory neurons that are capable of transmitting the sensation of pain consist of three major portions. The peripheral process (also known as the dendritic zone), which is composed of an arborization of free nerve endings, is the most distal segment of the sensory neuron. These free nerve endings serve as the receptor sites for the sensory stimulus.

**Figure 1-2** Local anesthetic is placed at some point between the pain stimulus and the brain (dynamite). The nerve impulse travels up to the point of local anesthetic application and then “dies,” never reaching the brain, and pain does not occur.
endings respond to stimulation produced in the tissues in which they lie, provoking an impulse that is transmitted centrally along the axon. The axon is a thin cable-like structure that may be quite long (the giant squid axon has been measured at 100 to 200 cm). At its mesial (or central) end is an arborization similar to that seen in the peripheral process. However, in this case the arborization forms synapses with various nuclei in the CNS to distribute incoming (sensory) impulses to their appropriate sites within the CNS for interpretation. The cell body is the third part of the neuron. In the sensory neuron described here, the cell body is located at a distance from the axon, the main pathway of impulse transmission in this nerve. The cell body of the sensory nerve therefore is not involved in the process of impulse transmission, its primary function being to provide vital metabolic support for the entire neuron (Fig. 1-3, B).

Nerve cells that conduct impulses from the CNS toward the periphery are termed motor neurons and are structurally different from the sensory neurons just described in that their cell body is interposed between the axon and dendrites. In motor neurons, the cell body not only is an integral component of the impulse transmission system but also provides metabolic support for the cell. Near its termination, the axon branches with each branch, ending as a bulbous axon terminal (or bouton). Axon terminals synapse with muscle cells (Fig. 1-3, A).
The Axon

The single nerve fiber, the axon, is a long cylinder of neural cytoplasm (axoplasm) encased in a thin sheath, the nerve membrane, or axolemma. Neurons have a cell body and a nucleus, as do all other cells; however, neurons differ from other cells in that they have an axonal process from which the cell body may be at a considerable distance. The axoplasm, a gelatinous substance, is separated from extracellular fluids by a continuous nerve membrane. In some nerves, this membrane is itself covered by an insulating lipid-rich layer of myelin.

Current thinking holds that both sensory nerve excitability and conduction are attributable to changes developing within the nerve membrane. The cell body and the axoplasm are not essential for nerve conduction. They are important, however. The metabolic support of the membrane is probably derived from the axoplasm.

The nerve (cell) membrane itself is approximately 70 to 80 Å thick. (An angstrom unit is 1/10,000 of a micrometer.) Figure 1-4 represents a currently acceptable configuration. All biological membranes are organized to block the diffusion of water-soluble molecules; to be selectively permeable to certain molecules via specialized pores or channels; and to transduce information through protein receptors responsive to chemical or physical stimulation by neurotransmitters or hormones (chemical) or light, vibration, or pressure (physical). The membrane is described as a

**Figure 1-4** A, Configuration of a biological membrane. B, Heterogeneous lipoprotein membrane as suggested by Singer and Nicholson.

(Redrawn from Covino BG, Vassalo HG: Local anesthetics: mechanisms of action and clinical use, New York, 1976, Grune & Stratton.)
flexible nonstretchable structure consisting of two layers of lipid molecules (bilipid layer of phospholipids) and associated proteins, lipids, and carbohydrates. The lipids are oriented with their hydrophilic (polar) ends facing the outer surface and their hydrophobic (nonpolar) ends projecting to the middle of the membrane (Fig. 1-4, A). Proteins are visualized as the primary organizational elements of membranes (Fig. 1-4, B). Proteins are classified as transport proteins (channels, carriers, or pumps) and receptor sites.

Channel proteins are thought to be continuous pores through the membrane, allowing some ions (Na⁺, K⁺, Ca²⁺) to flow passively, whereas other channels are gated, permitting ion flow only when the gate is open. The nerve membrane lies at the interface between extracellular fluid and axoplasm. It separates highly diverse ionic concentrations within the axon from those outside. The resting nerve membrane has an electrical resistance about 50 times greater than that of the intracellular and extracellular fluids, thus preventing the passage of sodium, potassium, and chloride ions down their concentration gradients. However, when a nerve impulse passes, electrical conductivity of the nerve membrane increases approximately 100-fold. This increase in conductivity permits the passage of sodium and potassium ions along their concentration gradients through the nerve membrane. It is the movement of these ions that provides an immediate source of energy for impulse conduction along the nerve.

TABLE 1-1 Classification of Peripheral Nerves According to Fiber Size and Physiologic Properties

<table>
<thead>
<tr>
<th>Fiber Class</th>
<th>Subclass</th>
<th>Diameter, µm</th>
<th>Conduction Velocity, m/s</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>alpha</td>
<td>6-22</td>
<td>30-120</td>
<td>Afferent to and efferent from muscles and joints</td>
<td>Motor, proprioception</td>
</tr>
<tr>
<td></td>
<td>beta</td>
<td>6-22</td>
<td>30-120</td>
<td>Afferent to and efferent from muscles and joints</td>
<td>Motor, proprioception</td>
</tr>
<tr>
<td></td>
<td>gamma</td>
<td>3-6</td>
<td>15-35</td>
<td>Efferent to muscle spindles</td>
<td>Muscle tone</td>
</tr>
<tr>
<td></td>
<td>delta</td>
<td>1-4</td>
<td>5-25</td>
<td>Afferent sensory nerves</td>
<td>Pain, temperature, touch</td>
</tr>
<tr>
<td>B</td>
<td>sC</td>
<td>&lt;3</td>
<td>3-15</td>
<td>Preganglionic sympathetic</td>
<td>Various autonomic functions</td>
</tr>
<tr>
<td></td>
<td>d gammaC</td>
<td>0.3-1.3</td>
<td>0.7-1.3</td>
<td>Postganglionic sympathetic</td>
<td>Various autonomic functions</td>
</tr>
</tbody>
</table>


Some nerve fibers are covered by an insulating lipid layer of myelin. In vertebrates, myelinated nerve fibers include all but the smallest of axons (Table 1-1). Myelinated nerve fibers (Fig. 1-5) are enclosed in spirally wrapped layers of lipoprotein myelin sheaths, which are actually a specialized form of Schwann cell. Although primarily lipid (75%), the myelin sheath also contains some protein (20%) and carbohydrate (5%). Each myelinated nerve fiber is enclosed in its own myelin sheath. The outermost layer of myelin consists of the Schwann cell cytoplasm and its nucleus. Constrictions are located at regular intervals (approximately every 0.5 to 3 mm) along the myelinated nerve fiber. These are nodes of Ranvier, and they form a gap between two adjoining Schwann cells and their myelin spirals. At these
Figure 1-5 Structure of a myelinated nerve fiber.

(Redrawn from de Jong RH: Local anesthetics, St Louis, 1994, Mosby.)

Figure 1-6 Types of Schwann cell sheaths.

(Redrawn from Wildsmith JAW: Peripheral nerve and anaesthetic drugs, Br J Anaesth 58:692-700, 1986.)
nodes, the nerve membrane is exposed directly to the extracellular medium.

Unmyelinated nerve fibers (Fig. 1-6) are also surrounded by a Schwann cell sheath. Groups of unmyelinated nerve fibers share the same sheath. The insulating properties of the myelin sheath enable a myelinated nerve to conduct impulses at a much faster rate than an unmyelinated nerve of equal size.

**Physiology of the Peripheral Nerves**

The function of a nerve is to carry messages from one part of the body to another. These messages, in the form of electrical action potentials, are called **impulses**. Action potentials are transient depolarizations of the membrane that result from a brief increase in the permeability of the membrane to sodium, and usually also from a delayed increase in its permeability to potassium. Impulses are initiated by chemical, thermal, mechanical, or electrical stimuli.

Once an impulse is initiated by a stimulus in any particular nerve fiber, the amplitude and shape of that impulse remain constant, regardless of changes in the quality of the stimulus or in its strength. The impulse remains constant without losing strength as it passes along the nerve because the energy used for its propagation is derived from energy that is released by the nerve fiber along its length and not solely from the initial stimulus. de Jong has described impulse conduction as being like the active progress of a spark along a fuse of gunpowder. Once lit, the fuse burns steadily along its length, with one burning segment providing the energy necessary to ignite its neighbor. Such is the situation with impulse propagation along a nerve.

**Electrophysiology of Nerve Conduction**

Following is a description of electrical events that occur within a nerve during the conduction of an impulse. Subsequent sections describe the precise mechanisms for each of these steps.

A nerve possesses a resting potential (Fig. 1-7, Step 1). This is a negative electrical potential of −70 mV that exists across the nerve membrane, produced by differing concentrations of ions on either side of the membrane (Table 1-2). The interior of the nerve is negative relative to the exterior.

**Step 1**

A stimulus excites the nerve, leading to the following sequence of events:

A  An initial phase of slow depolarization. The electrical potential within the nerve becomes slightly less negative (see Fig. 1-7, Step 1A).

B  When the falling electrical potential reaches a critical level, an extremely rapid phase of depolarization results. This is termed **threshold potential**, or **firing threshold** (see Fig. 1-7, Step 1B).

C  This phase of rapid depolarization results in a reversal of the electrical potential across the nerve membrane.
Figure 1-7  *Top*, Resting potential. Step 1, **A** and **B**, Slow depolarization to threshold. Step 1, **C**, Rapid depolarization. Step 2, Repolarization.

(see **Fig. 1-7, Step 1C**). The interior of the nerve is now electrically positive in relation to the exterior. An electrical potential of +40 mV exists on the interior of the nerve cell.\(^{11}\)
TABLE 1-2 Intracellular and Extracellular Ionic Concentrations

<table>
<thead>
<tr>
<th>Ion</th>
<th>Intracellular, mEq/L</th>
<th>Extracellular, mEq/L</th>
<th>Ratio (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (K⁺)</td>
<td>110-170</td>
<td>3-5</td>
<td>27:1</td>
</tr>
<tr>
<td>Sodium (Na⁺)</td>
<td>5-10</td>
<td>140</td>
<td>1:14</td>
</tr>
<tr>
<td>Chloride (Cl⁻)</td>
<td>5-10</td>
<td>110</td>
<td>1:11</td>
</tr>
</tbody>
</table>

Step 2

After these steps of depolarization, repolarization occurs (Fig. 1-7, Step 2). The electrical potential gradually becomes more negative inside the nerve cell relative to outside until the original resting potential of −70 mV is again achieved.

The entire process (Steps 1 and 2) requires 1 millisecond (msec); depolarization (Step 1) takes 0.3 msec; repolarization (Step 2) takes 0.7 msec.

Electrochemistry of Nerve Conduction

The preceding sequence of events depends on two important factors: the concentrations of electrolytes in the axoplasm (interior of the nerve cell) and extracellular fluids, and the permeability of the nerve membrane to sodium and potassium ions.

Table 1-2 shows the differing concentrations of ions found within neurons and in the extracellular fluids. Significant differences exist for ions between their intracellular and extracellular concentrations. These ionic gradients differ because the nerve membrane exhibits selective permeability.

Resting State

In its resting state, the nerve membrane is

- Slightly permeable to sodium ions (Na⁺)
- Freely permeable to potassium ions (K⁺)
- Freely permeable to chloride ions (Cl⁻)

Potassium remains within the axoplasm, despite its ability to diffuse freely through the nerve membrane and its concentration gradient (passive diffusion usually occurs from a region of greater concentration to one of lesser concentration), because the negative charge of the nerve membrane restrains the positively charged ions by electrostatic attraction.

Chloride remains outside the nerve membrane instead of moving along its concentration gradient into the nerve cell, because the opposing, nearly equal, electrostatic influence (electrostatic gradient from inside to outside) forces outward migration. The net result is no diffusion of chloride through the membrane.
Sodium migrates inwardly because both the concentration (greater outside) and the electrostatic gradient (positive ion attracted by negative intracellular potential) favor such migration. Only the fact that the resting nerve membrane is relatively impermeable to sodium prevents a massive influx of this ion.

Membrane Excitation

Depolarization

Excitation of a nerve segment leads to an increase in permeability of the cell membrane to sodium ions. This is accomplished by a transient widening of transmembrane ion channels sufficient to permit the unhindered passage of hydrated sodium ions. The rapid influx of sodium ions to the interior of the nerve cell causes depolarization of the nerve membrane from its resting level to its firing threshold of approximately −50 to −60 mV (see Fig. 1-7, Steps 1A and 1B). The firing threshold is actually the magnitude of the decrease in negative transmembrane potential that is necessary to initiate an action potential (impulse).

A decrease in negative transmembrane potential of 15 mV (e.g., from −70 to −55 mV) is necessary to reach the firing threshold; a voltage difference of less than 15 mV will not initiate an impulse. In a normal nerve, the firing threshold remains constant. Exposure of the nerve to a local anesthetic raises its firing threshold. Elevating the firing threshold means that more sodium must pass through the membrane to decrease the negative transmembrane potential to a level where depolarization occurs.

When the firing threshold is reached, membrane permeability to sodium increases dramatically and sodium ions rapidly enter the axoplasm. At the end of depolarization (the peak of the action potential), the electrical potential of the nerve is actually reversed; an electrical potential of +40 mV exists (see Fig. 1-7, Step 1C). The entire depolarization process requires approximately 0.3 msec.

Repolarization

The action potential is terminated when the membrane repolarizes. This is caused by the extinction (inactivation) of increased permeability to sodium. In many cells, permeability to potassium also increases, resulting in the efflux of K⁺, and leading to more rapid membrane repolarization and return to its resting potential (see Fig. 1-7, Step 2).

Movement of sodium ions into the cell during depolarization and subsequent movement of potassium ions out of the cell during repolarization are passive (not requiring the expenditure of energy), because each ion moves along its concentration gradient (higher → lower). After the return of the membrane potential to its original level (−70 mV), a slight excess of sodium exists within the nerve cell, along with a slight excess of potassium extracellularly. A period of metabolic activity then begins in which active transfer of sodium ions out of the cell occurs via the sodium pump. An expenditure of energy is necessary to move sodium ions out of the nerve cell against their concentration gradient; this energy comes from the oxidative metabolism of adenosine triphosphate (ATP). The same pumping mechanism is thought to be responsible for the active transport of potassium ions into the cell against their concentration gradient. The process of repolarization requires 0.7 msec.
Immediately after a stimulus has initiated an action potential, a nerve is unable, for a time, to respond to another stimulus regardless of its strength. This is termed the absolute refractory period, and it lasts for about the duration of the main part of the action potential. The absolute refractory period is followed by a relative refractory period, during which a new impulse can be initiated but only by a stronger than normal stimulus. The relative refractory period continues to decrease until the normal level of excitability returns, at which point the nerve is said to be repolarized.

During depolarization, a major proportion of ionic sodium channels are found in their open (O) state (thus permitting the rapid influx of Na\(^+\)). This is followed by a slower decline into a state of inactivation (I) of the channels to a nonconducting state. Inactivation temporarily converts the channels to a state from which they cannot open in response to depolarization (absolute refractory period). This inactivated state is slowly converted back, so that most channels are found in their closed (C) resting form when the membrane is repolarized (−70 mV). Upon depolarization, the channels change configuration, first to an open ion-conducting (O) state and then to an inactive nonconducting (I) state. Although both C and I states correspond to nonconducting channels, they differ in that depolarization can recruit channels to the conducting O state from C but not from I. Figure 1-8 describes the sodium channel transition stages.\(^{13}\)

**Membrane Channels**

Discrete aqueous pores through the excitable nerve membrane, called sodium (or ion) channels, are molecular structures that mediate its sodium permeability. A channel appears to be a lipoglycoprotein firmly situated in the membrane (see Fig. 1-4). It consists of an aqueous pore spanning the membrane that is narrow enough at least at one point to discriminate between sodium ions and others; Na\(^+\) passes through 12 times more easily than K\(^+\). The channel also includes a portion that changes configuration in response to changes in membrane potential, thereby gating the passage of ions through the pore (C, O, and I states are described). The presence of these channels helps explain membrane permeability or impermeability to certain ions. Sodium channels have an internal diameter of approximately 0.3 × 0.5 nm.\(^{14}\)
Figure 1-8 Sodium channel transition stages. Depolarization reverses resting membrane potential from interior negative (left) to interior positive (center). The channel proteins undergo corresponding conformational changes from resting state (closed) to ion-conducting stage (open). State changes continue from open (center) to inactive (right), where channel configuration assumes a different, but still impermeable, state. With repolarization, the inactivated refractory channel reverts to the initial resting configuration (left), ready for the next sequence.

Figure 1-9 Membrane channels are partially occluded; the nerve is at rest. Hydrated sodium ions (Na\(^+\)) are too large to pass through channels, although potassium ions (K\(^+\)) can pass through unimpeded.

A sodium ion is thinner than a potassium or chloride ion and therefore should diffuse freely down its concentration gradient through membrane channels into the nerve cell. However, this does not occur, because all these ions attract water molecules and thus become hydrated. Hydrated sodium ions have a
radius of 3.4 Å, which is approximately 50% greater than the 2.2 Å radius of potassium and chloride ions. Sodium ions therefore are too large to pass through narrow channels when a nerve is at rest (Fig. 1-9). Potassium and chloride ions can pass through these channels. During depolarization, sodium ions readily pass through the nerve membrane because configurational changes that develop within the membrane produce transient widening of these transmembrane channels to a size adequate to allow the unhindered passage of sodium ions down their concentration gradient into the axoplasm (transformation from the C to the O configuration). This concept can be visualized as the opening of a gate during depolarization that is partially occluding the channel in the resting membrane (C) (Fig. 1-10).

Evidence indicates that channel specificity exists in that sodium channels differ from potassium channels. The gates on the sodium channel are located near the external surface of the nerve membrane, whereas those on the potassium channel are located near the internal surface of the nerve membrane.

**Impulse Propagation**

After initiation of an action potential by a stimulus, the impulse must move along the surface of the axon. Energy for impulse propagation is derived from the nerve membrane in the following manner.

The stimulus disrupts the resting equilibrium of the nerve membrane; the transmembrane potential is reversed momentarily, with the interior of the cell changing from negative to positive, and the exterior changing from positive to negative. This new electrical equilibrium in this segment of nerve produces local currents that begin to flow between

**Figure 1-10** Membrane channels are open; depolarization occurs. Hydrated sodium ions (Na⁺) now pass unimpeded through the sodium channel.
the depolarized segment and the adjacent resting area. These local currents flow from positive to negative, extending for several millimeters along the nerve membrane.

As a result of this current flow, the interior of the adjacent area becomes less negative and its exterior less positive. Transmembrane potential decreases, approaching firing threshold for depolarization. When transmembrane potential is decreased by 15 mV from resting potential, a firing threshold is reached and rapid depolarization occurs. The newly depolarized segment sets up local currents in adjacent resting membrane, and the entire process starts anew.

Conditions in the segment that has just depolarized return to normal after the absolute and relative refractory periods. Because of this, the wave of depolarization can spread in only one direction. Backward (retrograde) movement is prevented by the inexcitable, refractory segment.

**Impulse Spread**

The propagated impulse travels along the nerve membrane toward the CNS. The spread of this impulse differs depending on whether or not a nerve is myelinated.

**Unmyelinated Nerves**

An unmyelinated nerve fiber is basically a long cylinder with a high–electrical resistance cell membrane surrounding a low-resistance conducting core of axoplasm, all of which is bathed in low-resistance extracellular fluid.

The high-resistance cell membrane and low-resistance intracellular and extracellular media produce a rapid decrease
Figure 1-11 Saltatory propagation. Comparison of impulse propagation in nonmyelinated (*upper*) and myelinated (*lower*) axons. In nonmyelinated axons, the impulse moves forward by sequential depolarization of short adjoining membrane segments. Depolarization in myelinated axons, on the other hand, is discontinuous; the impulse leaps forward from node to node. Note how much farther ahead the impulse is in the myelinated axon after four depolarization sequences.

(Redrawn from de Jong RH: Local anesthetics, St Louis, 1994, Mosby.)

in the density of current within a short distance of the depolarized segment. In areas immediately adjacent to this depolarized segment, local current flow may be adequate to initiate depolarization in the resting membrane. Farther away it will prove to be inadequate to achieve a firing threshold.
The spread of an impulse in an unmyelinated nerve fiber therefore is characterized as a relatively slow forward-creeping process (Fig. 1-11). The conduction rate in unmyelinated C fibers is 1.2 m/sec compared with 14.8 to 120 m/sec in myelinated A-alpha and A-delta fibers.  

Myelinated Nerves

Impulse spread within myelinated nerves differs from that in unmyelinated nerves because of the layer of insulating material separating the intracellular and extracellular charges. The farther apart are the charges, the smaller is the current necessary to charge the membrane. Local currents thus can travel much farther in a myelinated nerve than in an unmyelinated nerve before becoming incapable of depolarizing the nerve membrane ahead of it.

Impulse conduction in myelinated nerves occurs by means of current leaps from node to node, a process termed saltatory conduction (see Fig. 1-11) (saltare is the Latin verb “to leap”). This form of impulse conduction proves to be much faster and more energy efficient than that employed in unmyelinated nerves. The thickness of the myelin sheath increases with increasing diameter of the axon. In addition, the distance between adjacent nodes of Ranvier increases with greater axonal diameter. Because of these two factors, saltatory conduction is more rapid in a thicker axon.

Saltatory conduction usually progresses from one node to the next in a stepwise manner. However, it can be demonstrated that the current flow at the next node still exceeds that necessary to reach the firing threshold of the nodal membrane. If conduction of an impulse is blocked at one node, the local current skips over that node and proves adequate to raise the membrane potential at the next node to its firing potential, producing depolarization. A minimum of perhaps 8 to 10 mm of nerve must be covered by anesthetic solution to ensure thorough blockade.

Mode and Site of Action of Local Anesthetics

How and where local anesthetics alter the processes of impulse generation and transmission needs to be discussed. It is possible for local anesthetics to interfere with the excitation process in a nerve membrane in one or more of the following ways:

1 Altering the basic resting potential of the nerve membrane

2 Altering the threshold potential (firing level)

3 Decreasing the rate of depolarization

4 Prolonging the rate of repolarization

It has been established that the primary effects of local anesthetics occur during the depolarization phase of the action potential. These effects include a decrease in the rate of depolarization, particularly in the phase of slow depolarization. Because of this, cellular depolarization is not sufficient to reduce the membrane potential of a nerve fiber to its firing level, and a propagated action potential does not develop. There is no accompanying change in the rate of repolarization.
Where Do Local Anesthetics Work?

The nerve membrane is the site at which local anesthetics exert their pharmacologic actions. Many theories have been promulgated over the years to explain the mechanism of action of local anesthetics, including the acetylcholine, calcium displacement, and surface charge theories. The acetylcholine theory stated that acetylcholine was involved in nerve conduction, in addition to its role as a neurotransmitter at nerve synapses. No evidence indicates that acetylcholine is involved in neural transmission along the body of the neuron. The calcium displacement theory, once popular, maintained that local anesthetic nerve block was produced by the displacement of calcium from some membrane site that controlled permeability to sodium. Evidence that varying the concentration of calcium ions bathing a nerve does not affect local anesthetic potency has diminished the credibility of this theory. The surface charge (repulsion) theory proposed that local anesthetics act by binding to the nerve membrane and changing the electrical potential at the membrane surface. Cationic (RNH+) drug molecules were aligned at the membrane–water interface, and because some of the local anesthetic molecules carried a net positive charge, they made the electrical potential at the membrane surface more positive, thus decreasing the excitability of the nerve by increasing the threshold potential. Current evidence indicates that the resting potential of the nerve membrane is unaltered by local anesthetics (they do not become hyperpolarized), and that conventional local anesthetics act within membrane channels rather than at the membrane surface. Also, the surface charge theory cannot explain the activity of uncharged anesthetic molecules in blocking nerve impulses (e.g., benzocaine).

Two other theories, membrane expansion and specific receptor, are given credence today. Of the two, the specific receptor theory is more widely held.

The membrane expansion theory states that local anesthetic molecules diffuse to hydrophobic regions of excitable membranes, producing a general disturbance of the bulk membrane structure, expanding some critical region(s) in the membrane, and preventing an increase in permeability to sodium ions. Local anesthetics that are highly lipid soluble can easily penetrate the lipid portion of the cell membrane, producing a change in configuration of the lipoprotein matrix of the nerve membrane. This results in a decreased diameter of sodium channels, which leads to inhibition of both sodium conductance and neural excitation (Fig. 1-12). The membrane expansion theory serves as a possible explanation for the local anesthetic activity of a drug such as benzocaine, which does not exist in cationic form yet still exhibits potent topical anesthetic activity. It has been demonstrated that nerve membranes, in fact, do expand and become more fluid when exposed to local anesthetics. However, no direct evidence suggests that nerve conduction is entirely blocked by membrane expansion per se.

The specific receptor theory, the most favored today, proposes that local anesthetics act by binding to specific receptors on the sodium channel (Fig. 1-13). The action of the drug is direct, not mediated by some change in the general properties of the cell membrane. Both biochemical and electrophysiologic studies have indicated that a specific receptor site for local anesthetics exists in the sodium channel either on its external surface or on the internal axoplasmic surface. Once the local anesthetic has gained access to the receptors, permeability to sodium ions is decreased or eliminated, and nerve conduction is interrupted.
Local anesthetics are classified by their ability to react with specific receptor sites in the sodium channel. It appears that drugs can alter nerve conduction in at least four sites within the sodium channel (see Fig. 1-13):

1. Within the sodium channel (tertiary amine local anesthetics)
2. At the outer surface of the sodium channel (tetrodotoxin, saxitoxin)
3. At the activation or the inactivation gate (scorpion venom)

Table 1-3 is a biological classification of local anesthetics based on their site of action and the active form of the compound. Drugs in Class C exist only in the uncharged form (RN), whereas Class D drugs exist in both charged and uncharged forms. Approximately 90% of the blocking effects of Class D drugs are caused by the cationic form of the drug; only 10% of blocking action is produced by the base (Fig. 1-14).
TABLE 1-3 Classification of Local Anesthetic Substances According to Biological Site and Mode of Action

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
<th>Chemical Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Agents acting at receptor site on external surface of nerve membrane</td>
<td>Biotoxins (e.g., tetrodotoxin, saxitoxin)</td>
</tr>
<tr>
<td>Class B</td>
<td>Agents acting at receptor site on internal surface of nerve membrane</td>
<td>Quaternary ammonium analogs of lidocaine, Scorpion venom</td>
</tr>
<tr>
<td>Class C</td>
<td>Agents acting by a receptor-independent physico-chemical mechanism</td>
<td>Benzocaine</td>
</tr>
<tr>
<td>Class D</td>
<td>Agents acting by combination of receptor and receptor-independent mechanisms</td>
<td>Most clinically useful local anesthetic agents (e.g., articaine, lidocaine, mepivacaine, prilocaine)</td>
</tr>
</tbody>
</table>


Myelinated Nerve Fibers

One additional factor should be considered with regard to the site of action of local anesthetics in myelinated nerves. The myelin sheath insulates the axon both electrically and pharmacologically. The only site at which molecules of local anesthetic have access to the nerve membrane is at the nodes of Ranvier, where sodium channels are found in abundance. Ionic changes that develop during impulse conduction arise only at the nodes.

Because an impulse may skip over or bypass one or two blocked nodes and continue on its way, it is necessary for at least two or three nodes immediately adjacent to the anesthetic solution to be blocked to ensure effective anesthesia—a length of approximately 8 to 10 mm.
Figure 1-13  **A**, Tertiary amine local anesthetics inhibit the influx of sodium during nerve conduction by binding to a receptor within the sodium channel (R-LA). This blocks the normal activation mechanism (O gate configuration, depolarization) and also promotes movement of the activation and inactivation gates (m and h) to a position resembling that in the inactivated state (I). **B**, Biotoxins (R-T) block the influx of sodium at an outer surface receptor; various venoms do it by altering the activity of the activation and inactivation gates; and benzocaine (R-B) does it by expanding the membrane. **C**, Channel in the closed configuration.

(Redrawn from Pallasch TJ: Dent Drug Serv Newsletter 4:25, 1983.)
Figure 1-14 Channel entry. On the left is an open channel, inward permeant to sodium ion. The center channel is in the resting closed configuration; although impermeant to sodium ion here, the channel remains voltage responsive. The channel on the right, although in open configuration, is impermeant because it has local anesthetic cation bound to the gating receptor site. Note that local anesthetic enters the channel from the axoplasmic (lower) side; the channel filter precludes direct entry via the external mouth. Local anesthetic renders the membrane impermeant to sodium ion, hence inexcitable by local action currents.

(Redrawn from de Jong RH: Local anesthetics, St Louis, 1994, Mosby.)

Sodium channel densities differ in myelinated and unmyelinated nerves. In small unmyelinated nerves, the density of sodium channels is about 35/µm, whereas at the nodes of Ranvier in myelinated fibers, it may be as high as 20,000/µm. On an average nerve length basis, relatively few sodium channels are present in unmyelinated nerve membranes. For example, in the garfish olfactory nerve, the ratio of sodium channels to phospholipid molecules is 1:60,000, corresponding to a mean distance between channels of 0.2 µm, whereas at densely packed nodes of Ranvier, the channels are separated by only 70 Å. 27,28

How Local Anesthetics Work

The primary action of local anesthetics in producing a conduction block is to decrease the permeability of ion channels to sodium ions (Na⁺). Local anesthetics selectively inhibit the peak permeability of sodium,
whose value is normally about five to six times greater than the minimum necessary for impulse conduction (e.g., there is a safety factor for conduction of $5 \times \text{ to } 6 \times$). Local anesthetics reduce this safety factor, decreasing both the rate of rise of the action potential and its conduction velocity. When the safety factor falls below unity, conduction fails and nerve block occurs.

Local anesthetics produce a very slight, virtually insignificant decrease in potassium ($K^+$) conductance through the nerve membrane.

Calcium ions ($Ca^{++}$), which exist in bound form within the cell membrane, are thought to exert a regulatory role on the movement of sodium ions across the nerve membrane. Release of bound calcium ions from the ion channel receptor site may be the primary factor responsible for increased sodium permeability of the nerve membrane. This represents the first step in nerve membrane depolarization. Local anesthetic molecules may act through competitive antagonism with calcium for some site on the nerve membrane.

The following sequence is a proposed mechanism of action of local anesthetics[^1]:

1. Displacement of calcium ions from the sodium channel receptor site, which permits ...  
2. Binding of the local anesthetic molecule to this receptor site, which produces ...  
3. Blockade of the sodium channel, and a ...  
4. Decrease in sodium conductance, which leads to ...  
5. Depression of the rate of electrical depolarization, and ...  
6. Failure to achieve the threshold potential level, along with ...  
7. Lack of development of propagated action potentials, which is called ...  

The mechanism whereby sodium ions gain entry to the axoplasm of the nerve, thereby initiating an action potential, is altered by local anesthetics. The nerve membrane remains in a polarized state because the ionic movements responsible for the action potential fail to develop. Because the membrane's electrical potential remains unchanged, local currents do not develop, and the self-perpetuating mechanism of impulse propagation is stalled. An impulse that arrives at a blocked nerve segment is stopped because it is unable to release the energy necessary for its continued propagation. Nerve block produced by local anesthetics is called a nondepolarizing nerve block.

**Active Forms of Local Anesthetics**

**Local Anesthetic Molecules**

Most injectable local anesthetics are tertiary amines. Only a few (e.g., prilocaine, hexylcaine) are secondary amines. The typical local anesthetic structure is shown in Figures 1-15 and 1-16.
The lipophilic part is the largest portion of the molecule. Aromatic in structure, it is derived from benzoic acid, aniline, or thiophene (articaine). All local anesthetics are amphipathic, that is, they possess both lipophilic and hydrophilic characteristics, generally at opposite ends of the molecule. The hydrophilic part is an amino derivative of ethyl alcohol or acetic acid. Local anesthetics without a hydrophilic part are not suited for injection but are good topical anesthetics (e.g., benzocaine). The anesthetic structure is completed by an intermediate hydrocarbon chain containing an ester or an amide linkage. Other chemicals, especially histamine blockers and anticholinergics, share this basic structure with local anesthetics and commonly exhibit weak local anesthetic properties.

Local anesthetics may be classified as amino esters or amino amides according to their chemical linkages. The nature of the linkage is important in defining several properties of the local anesthetic, including the basic mode of biotransformation. Ester-linked local anesthetics (e.g., procaine) are readily hydrolyzed in aqueous solution. Amide-linked local anesthetics (e.g., lidocaine) are relatively resistant to hydrolysis. A greater percentage of an amide-linked drug than of an ester-linked drug is excreted unchanged in the urine. Procainamide, which is procaine with an amide linkage replacing the ester linkage, is as potent a local anesthetic as procaine, yet because of its amide linkage, it is hydrolyzed much more slowly. Procaine is hydrolyzed in plasma in only a few minutes, but just approximately 10% of procainamide is hydrolyzed in 1 day.
As prepared in the laboratory, local anesthetics are basic compounds that are poorly soluble in water and unstable on exposure to air. Their pKₐ values range from 7.5 to 10. In this form, they have little or no clinical value. However, because they are weakly basic, they combine readily with acids to form local anesthetic salts, in which form they are quite soluble in water and comparatively stable. Thus local anesthetics used for injection are dispensed as acid salts, most commonly the hydrochloride salt (e.g., lidocaine HCl, articaine HCl), dissolved in sterile water or saline.

Figure 1-16 Chemical configuration of local anesthetics.

(From Yagiela JA, Neidle EA, Dowd FJ: Pharmacology and therapeutics for dentistry, ed 6, St Louis, 2010, Mosby.)
It is well known that the pH of a local anesthetic solution (as well as the pH of the tissue into which it is injected) greatly influences its nerve-blocking action. Acidification of tissue decreases local anesthetic effectiveness. Inadequate anesthesia results when local anesthetics are injected into inflamed or infected areas. The inflammatory process produces acidic products: The pH of normal tissue is 7.4; the pH of an inflamed area is 5 to 6. Local anesthetics containing epinephrine or other vasopressors are acidified by the manufacturer to inhibit oxidation of the vasopressor (p. 18). The pH of solutions without epinephrine is about 6.5; epinephrine-containing solutions have a pH of about 3.5. Clinically, this lower pH is more likely to produce a burning sensation on injection, as well as a slightly slower onset of anesthesia.

Elevating the pH (alkalinization) of a local anesthetic solution speeds its onset of action, increases its clinical effectiveness, and makes its injection more comfortable. However, the local anesthetic base, because it is unstable, precipitates out of alkalinized solutions, making these preparations ill-suited for clinical use. Buffered (e.g., carbonated) local anesthetics have received much attention in recent years both in medicine and, more recently, in dentistry. Sodium bicarbonate or carbon dioxide (CO₂) added to the anesthetic solution immediately before injection provides greater comfort and more rapid onset of anesthesia (see Chapter 19). The use of buffered local anesthetics in dentistry is reviewed in depth in Chapter 20.

Despite potentially wide pH variation in extracellular fluids, the pH at the interior of a nerve remains stable. Normal functioning of a nerve therefore is affected very little by changes in the extracellular environment. However, the ability of a local anesthetic to block nerve impulses is profoundly altered by changes in extracellular pH.

**Dissociation of Local Anesthetics**

As discussed, local anesthetics are available as acid salts (usually hydrochloride) for clinical use. The local anesthetic salt, both water soluble and stable, is dissolved in sterile water or saline. In this solution, it exists simultaneously as uncharged molecules (RN), also called the base, and as positively charged molecules (RNH⁺), called the cation.

\[ \text{RNH}^+ \rightleftharpoons \text{RN} + \text{H}^+ \]

The relative proportion of each ionic form in the solution varies with the pH of the solution or surrounding tissues. In the presence of a high concentration of hydrogen ions (low pH), the equilibrium shifts to the left, and most of the anesthetic solution exists in cationic form:

\[ \text{RNH}^+ > \text{RN} + \text{H}^+ \]

As hydrogen ion concentration decreases (higher pH), the equilibrium shifts toward the free base form:

\[ \text{RNH}^+ < \text{RN} + \text{H}^+ \]

The relative proportion of ionic forms also depends on the pKₐ, or dissociation constant, of the specific local anesthetic. The pKₐ is a measure of the affinity of a molecule for hydrogen ions (H⁺). When the pH of
the solution has the same value as the $pK_a$ of the local anesthetic, exactly 50% of the drug exists in the RNH\(^+\) form and 50% in the RN form. The percentage of drug existing in either form can be determined from the Henderson-Hasselbalch equation.

Table 1-4 lists the $pK_a$ values for commonly used local anesthetics.

### Actions on Nerve Membranes

The two factors involved in the action of a local anesthetic are (1) diffusion of the drug through the nerve sheath, and (2) binding at the receptor site in the ion channel. The uncharged, lipid-soluble, free base form (RN) of the anesthetic is responsible for diffusion through the nerve sheath. This process is explained in the following example:

#### Table 1-4 Dissociation Constants ($pK_a$) of Local Anesthetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>$pK_a$</th>
<th>% Base (RN) at pH 7.4</th>
<th>Approximate Onset of Action, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzocaine</td>
<td>3.5</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>7.7</td>
<td>33</td>
<td>2-4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.7</td>
<td>29</td>
<td>2-4</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.7</td>
<td>25</td>
<td>2-4</td>
</tr>
<tr>
<td>Articaine</td>
<td>7.8</td>
<td>29</td>
<td>2-4</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>7.9</td>
<td>25</td>
<td>2-4</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.1</td>
<td>17</td>
<td>2-4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>17</td>
<td>5-8</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8.6</td>
<td>7</td>
<td>10-15</td>
</tr>
<tr>
<td>Cocaine</td>
<td>8.6</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>8.7</td>
<td>6</td>
<td>6-12</td>
</tr>
<tr>
<td>Propoxycaine</td>
<td>8.9</td>
<td>4</td>
<td>9-14</td>
</tr>
<tr>
<td>Procaine</td>
<td>9.1</td>
<td>2</td>
<td>14-18</td>
</tr>
<tr>
<td>Procainamide</td>
<td>9.3</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

Figure 1-17 Mechanism of action of the local anesthetic molecule. Anesthetic $pK_a$ of 7.9; tissue pH of 7.4.
One thousand molecules of a local anesthetic with a pKₐ of 7.9 are injected into the tissues outside a nerve. The tissue pH is normal (7.4) (Fig. 1-17).

From Table 1-4 and the Henderson-Hasselbalch equation, it can be determined that at normal tissue pH, 75% of local anesthetic molecules are present in the cationic form (RNH⁺) and 25% in the free base form (RN).

In theory then, all 250 lipophilic RN molecules will diffuse through the nerve sheath to reach the interior (axoplasm) of the neuron.

When this happens, the extracellular equilibrium between RNH⁺ ⇌ RN has been disrupted by passage of the free base forms into the neuron. The remaining 750 extracellular RNH⁺ molecules will now reequilibrate according to the tissue pH and the pKₐ of the drugs:

\[ \text{RNH}^+ (570) \rightleftharpoons \text{RN} (180) + H^+ \]

The 180 newly created lipophilic RN molecules diffuse into the cell, starting the entire process (Step 4) again. Theoretically, this will continue until all local anesthetic molecules diffuse into the axoplasm.

The reality, however, is somewhat different. Not all the local anesthetic molecules will eventually reach the interior of the nerve, because of the process of diffusion (drugs will diffuse in all possible directions, not just toward the nerve), and because some will be absorbed into blood vessels and extracellular soft tissues at the injection site.

The inside of the nerve should be viewed next. After penetration of the nerve sheath and entry into the axoplasm by the lipophilic RN form of the anesthetic, reequilibration takes place inside the nerve, because a local anesthetic cannot exist in only the RN form at an intracellular pH of 7.4. Seventy-five percent of those RN molecules present within the axoplasm revert into the RNH⁺ form; the remaining 25% of molecules remain in the uncharged RN form.

From the axoplasmic side, the RNH⁺ ions enter into the sodium channels, bind to the channel receptor site, and ultimately are responsible for the conduction blockade that results (see Figs. 1-13 and 1-14).

Of the two factors—diffusibility and binding—responsible for local anesthetic effectiveness, the former is extremely important in actual practice. The ability of a local anesthetic to diffuse through the tissues surrounding a nerve is of critical significance, because in clinical situations the local anesthetic cannot be applied directly to the nerve membrane, as it can in a laboratory setting. Local anesthetic solutions better able to diffuse through soft tissue provide an advantage in clinical practice.

A local anesthetic with a high pKₐ value has very few molecules available in the RN form at a tissue pH of 7.4. The onset of anesthetic action of this drug is slow because too few base molecules are available to
diffuse through the nerve membrane (e.g., procaine, with a \( pK_a \) of 9.1). The rate of onset of anesthetic action is related to the \( pK_a \) of the local anesthetic (see Table 1-4).

A local anesthetic with a lower \( pK_a \) (<7.5) has a greater number of lipophilic free base molecules available to diffuse through the nerve sheath; however, the anesthetic action of this drug is inadequate because at an intracellular pH of 7.4, only a very small number of base molecules dissociate back to the cationic form necessary for binding at the receptor site.

In actual clinical situations with the local anesthetics currently available, the pH of the extracellular fluid determines the ease with which a local anesthetic moves from the site of its administration into the axoplasm of the nerve cell. The intracellular pH remains stable and independent of the extracellular pH, because hydrogen ions (\( H^+ \)), such as the local anesthetic cations (\( RNH^+ \)), do not readily diffuse through tissues. The pH of extracellular fluid therefore may differ from that of the nerve membrane. The ratio of anesthetic cations to uncharged base molecules (\( RNH^+ / RN \)) also may vary greatly at these sites.

Differences in extracellular

**Figure 1-18** Effect of decreased tissue pH on the actions of a local anesthetic.
and intracellular pH are highly significant in pain control when inflammation or infection is present. The effect of a decrease in tissue pH on the actions of a local anesthetic is described in Figure 1-18. This can be compared with the example in Figure 1-17, involving normal tissue pH:

1. Approximately 1000 molecules of a local anesthetic with a pK\textsubscript{a} of 7.9 are deposited outside a nerve. The tissue is inflamed and infected and has a pH of 6.

2. At this tissue pH, approximately 99% of local anesthetic molecules are present in the charged cationic (RNH\textsuperscript{+}) form, with approximately 1% in the lipophilic free base (RN) form.

3. Approximately 10 RN molecules diffuse across the nerve sheath to reach the interior of the cell (contrasting with 250 RN molecules in the healthy example). The pH of the interior of the nerve cell remains normal (e.g., 7.4).

4. Extracellularly, the equilibrium between RNH\textsuperscript{+} = RN, which has been disrupted, is reestablished. The relatively few newly created RN molecules diffuse into the cell, starting the entire process again. However, a sum total of fewer RN molecules succeed in eventually crossing the nerve sheath than would succeed at a normal pH because of greatly increased absorption of anesthetic molecules into the blood vessels in the region (increased vascularity is noted in the area of inflammation and infection).

5. After penetration of the nerve sheath by the base form, reequilibrium occurs inside the nerve. Approximately 75% of the molecules present intracellularly revert to the cationic form (RNH\textsuperscript{+}), 25% remaining in the uncharged free base form (RN).

6. The cationic molecules bind to receptor sites within the sodium channel, resulting in conduction blockade.

Adequate blockade of the nerve is more difficult to achieve in inflamed or infected tissues because of the relatively small number of molecules able to cross the nerve sheath (RN) and the increased absorption of remaining anesthetic molecules into dilated blood vessels in this region. Although it presents a potential problem in all aspects of dental practice, this situation is seen most often in endodontics. Possible remedies are described in Chapter 16.

Clinical Implications of pH and Local Anesthetic Activity

Most commercially prepared solutions of local anesthetics without a vasoconstrictor have a pH between 5.5 and 7. When injected into tissue, the vast buffering capacity of tissue fluids returns the pH at the injection site to a normal 7.4. Local anesthetic solutions containing a vasopressor (e.g., epinephrine) are acidified by the manufacturer through the addition of sodium (meta)bisulfite to retard oxidation of the vasoconstrictor, thereby prolonging the period of effectiveness of the drug. (See Chapter 3 for a discussion of the appropriate use of vasoconstrictors in local anesthetics.)
Epinephrine may be added to a local anesthetic solution immediately before its administration without the addition of antioxidants; however, if the solution is not used in a short time, it will oxidize, slowly turning yellow then brown (much like a sliced apple oxidizing).

Rapid oxidation of the vasopressor may be delayed, thereby increasing the shelf life of the product, through the addition of antioxidants. Sodium bisulfite in a concentration between 0.05% and 0.1% is commonly used. A 2% solution of lidocaine HCl, with a pH of 6.8, is acidified to 4.2 by the addition of sodium bisulfite.

Even in this situation, the enormous buffering capacity of the tissues tends to maintain a normal tissue pH; however, it does require a longer time to do so after injection of a pH 4.2 solution than with a pH 6.8 solution. During this time, the local anesthetic is not able to function at its full effectiveness, resulting in a slower onset of clinical action for local anesthetics with vasoconstrictors compared with their plain counterparts.

Local anesthetics are clinically effective on both axons and free nerve endings. Free nerve endings lying below intact skin may be reached only by injection of anesthetic beneath the skin. Intact skin forms an impenetrable barrier to the diffusion of local anesthetics. EMLA (eutectic mixture of local anesthetics lidocaine and prilocaine) enables local anesthetics to penetrate intact skin, albeit slowly.35

Mucous membranes and injured skin (e.g., burns, abrasions) lack the protection afforded by intact skin, permitting topically applied local anesthetics to diffuse through to reach free nerve endings. Topical anesthetics can be employed effectively wherever skin is no longer intact because of injury, as well as on mucous membranes (e.g., cornea, gingiva, pharynx, trachea, larynx, esophagus, rectum, vagina, bladder).36

The buffering capacity of mucous membrane is poor; thus topical application of a local anesthetic with a pH between 5.5 and 6.5 lowers the regional pH to below normal, and less local anesthetic base is formed. Diffusion of the drug across the mucous membrane to free nerve endings is limited, and nerve block is ineffective. Increasing the pH of the drug provides more RN form, thereby increasing the potency of the topical anesthetic; however, the drug in this form is more rapidly oxidized. The effective shelf life of the local anesthetic is decreased as the pH of the drug is increased.30

To enhance the clinical efficacy of topical anesthetics, a more concentrated form of the drug is commonly used (5% or 10% lidocaine) than for injection (2% lidocaine). Although only a small percentage of the drug is available in the base form, raising the concentration provides additional RN molecules for diffusion and dissociation to the active cation form at free nerve endings.

Some topical anesthetics (e.g., benzocaine) are not ionized in solution; thus their anesthetic effectiveness is unaffected by pH. Because of the poor water solubility of benzocaine, its absorption from the site of application is minimal, and systemic reactions (e.g., overdose) are rarely encountered.
Kinetics of Local Anesthetic Onset And Duration of Action

Barriers to Diffusion of the Solution

A peripheral nerve is composed of hundreds to thousands of tightly packed axons. These axons are protected, supported, and nourished by several layers of fibrous and elastic tissues. Nutrient blood vessels and lymphatics course throughout the layers.

Individual nerve fibers (axons) are covered with, and are separated from each other by, the endoneurium. The perineurium then binds these nerve fibers together into bundles called fasciculi. The radial nerve, located in the wrist, contains between 5 and 10 fasciculi. Each fasciculus contains between 500 and 1000 individual nerve fibers. Five thousand nerve fibers occupy approximately 1 mm$^2$ of space.

The thickness of the perineurium varies with the diameter of the fasciculus it surrounds. The thicker the perineurium, the slower the rate of local anesthetic diffusion across it. The innermost layer of perineurium is the perilemma. It is covered with a smooth mesothelial membrane. The perilemma represents the main barrier to diffusion into a nerve.

Fasciculi are contained within a loose network of areolar connective tissue called the epineurium. The epineurium constitutes between 30% and 75% of the total cross-section of a nerve. Local anesthetics are readily able to diffuse through the epineurium because of its loose consistency. Nutrient blood vessels and lymphatics traverse the epineurium. These vessels absorb local anesthetic molecules, removing them from the site of injection.

The outer layer of the epineurium surrounding the nerve is denser and is thickened, forming what is termed the epineural sheath or nerve sheath. The epineural sheath does not constitute a barrier to diffusion of local anesthetic into a nerve.

Table 1-5 summarizes the layers of a typical peripheral nerve.

Induction of Local Anesthesia

Following administration of a local anesthetic into the soft tissues near a nerve, molecules of the local anesthetic traverse the distance from one site to another according to their concentration gradient. During the induction phase of anesthesia, the local anesthetic moves from its extraneural site of deposition toward the nerve (as well as in all other possible directions). This process is termed diffusion. It is the unhindered migration of molecules or ions through a fluid medium under the influence of the concentration gradient. Penetration of an anatomic barrier to diffusion occurs when a drug passes through a tissue that tends to restrict free molecular movement. The perineurium is the greatest barrier to penetration of local anesthetics.

Diffusion

The rate of diffusion is governed by several factors, the most significant of which is the concentration
Figure 1-19  **A**, Composition of nerve fibers and bundles within a peripheral nerve.  **B**, In a large peripheral nerve (containing hundreds or thousands of axons), local anesthetic solution must diffuse inward toward the nerve core from the extraneural site of injection. Local anesthetic molecules are removed by tissue uptake while tissue fluid mixes with the carrier solvent. This results in gradual dilution of the local anesthetic solution as it penetrates the nerve toward the core. A concentration gradient occurs during induction so that the outer mantle fibers are solidly blocked, whereas the inner core fibers are not yet blocked. Not only are core fibers exposed to a lower local anesthetic concentration, but the drug arrives later. Delay depends on the tissue mass to be penetrated and the diffusivity of the local anesthetic.

(Redrawn from **B**, de Jong RH: Local anesthetics, St Louis, 1994, Mosby.)

gradient. The greater the initial concentration of the local anesthetic, the faster the diffusion of its molecules and the more rapid its onset of action.
TABLE 1-5 Organization of a Peripheral Nerve

<table>
<thead>
<tr>
<th>Structure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve fiber</td>
<td>Single nerve cell</td>
</tr>
<tr>
<td>Endoneurium</td>
<td>Covers each nerve fiber</td>
</tr>
<tr>
<td>Fasciculi</td>
<td>Bundles of 500 to 1000 nerve fibers</td>
</tr>
<tr>
<td>Perineurium*</td>
<td>Covers fasciculi</td>
</tr>
<tr>
<td>Perilemma*</td>
<td>Innermost layer of perineurium</td>
</tr>
<tr>
<td>Epineurium</td>
<td>Alveolar connective tissue supporting fasciculi and carrying nutrient vessels</td>
</tr>
<tr>
<td>Epineural sheath</td>
<td>Outer layer of epineurium</td>
</tr>
</tbody>
</table>

* The perineurium and perilemma constitute the greatest anatomic barriers to diffusion in a peripheral nerve.

Fasciculi that are located near the surface of the nerve are termed mantle bundles (Fig. 1-19, A). Mantle bundles are the first ones reached by the local anesthetic and are exposed to a higher concentration of it. Mantle bundles usually are blocked completely shortly after injection of a local anesthetic (Fig. 1-19, B).

Fasciculi found closer to the center of the nerve are called core bundles. Core bundles are contacted by a local anesthetic only after much delay and by a lower anesthetic concentration because of the greater distance that the solution must traverse and the greater number of barriers it must cross.

As the local anesthetic diffuses into the nerve, it becomes increasingly diluted by tissue fluids with some being absorbed by capillaries and lymphatics. Ester anesthetics undergo almost immediate enzymatic hydrolysis. Thus core fibers are exposed to a decreased concentration of local anesthetic, a fact that may explain the clinical situation of inadequate pulpal anesthesia developing in the presence of subjective symptoms of adequate soft tissue anesthesia. Complete conduction blockade of all nerve fibers in a peripheral nerve requires that an adequate volume, as well as an adequate concentration, of the local anesthetic be deposited. In no clinical situation are 100% of the fibers within a peripheral nerve blocked, even in cases of clinically excellent pain control. Fibers near the surface of the nerve (mantle fibers) tend to innervate more proximal regions (e.g., the molar area with an inferior alveolar nerve block), whereas fibers in the core bundles innervate the more distal points of nerve distribution (e.g., the incisors and canine with an inferior alveolar block).

**Blocking Process**

After deposition of local anesthetic as close to the nerve as possible, the solution diffuses in all directions according to prevailing concentration gradients. A portion of the injected local anesthetic diffuses toward the nerve and into the nerve. However, a significant portion of the injected drug also diffuses away from the nerve. The following reactions then occur:

1. Some of the drug is absorbed by nonneural tissues (e.g., muscle, fat).
2. Some is diluted by interstitial fluid.
3. Some is removed by capillaries and lymphatics from the injection site.
4. Ester-type anesthetics are hydrolyzed.
The sum total effect of these factors is to decrease the local anesthetic concentration outside the nerve; however, the concentration of local anesthetic within the nerve continues to rise as diffusion progresses. These processes continue until an equilibrium results between intraneural and extraneural concentrations of anesthetic solution.

**Induction Time**

*Induction time* is defined as the period from deposition of the anesthetic solution to complete conduction blockade. Several factors control the induction time of a given drug. Those under the operator's control are the concentration of the drug and the pH of the local anesthetic solution. Factors not under the clinician's control include the diffusion constant of the anesthetic drug and the anatomic diffusion barriers of the nerve.

**Physical Properties and Clinical Actions**

Other physicochemical factors of a local anesthetic may influence its clinical characteristics.

The effect of the *dissociation constant* (pK\(_a\)) on the rate of onset of anesthesia has been described. Although both molecular forms of the anesthetic are important in neural blockade, drugs with a lower pK\(_a\) possess a more rapid onset of action than those with a higher pK\(_a\).\(^{39}\)

*Lipid solubility* of a local anesthetic appears to be related to its intrinsic potency. The estimated lipid solubilities of various local anesthetics are presented in Table 1-6. Greater lipid solubility permits the anesthetic to penetrate the nerve membrane (which itself is 90% lipid) more easily. This is reflected biologically in increased potency of the anesthetic. Local anesthetics with greater lipid solubility produce more effective conduction blockade at lower concentrations (lower percentage solutions or smaller volumes deposited) than is produced by less lipid-soluble local anesthetics.

The degree of *protein binding* of the local anesthetic molecule is responsible for the duration of anesthetic activity. After penetration of the nerve sheath, a reequilibrium occurs between the base and cationic forms of the local anesthetic according to the Henderson-Hasselbach equation. Now, in the sodium channel itself, RNH\(^+\) ions bind at the receptor site. Proteins constitute approximately 10% of the nerve membrane, and local anesthetics (e.g., etidocaine, ropivacaine, bupivacaine) possessing a greater degree of protein binding (see Table 1-6) than others (e.g., procaine) appear to attach more securely to the protein receptor sites and to possess a longer duration of clinical activity.\(^{40}\)

*Vasoactivity* affects both the anesthetic potency and the duration of anesthesia provided by a drug. Injection of local anesthetics, such as procaine, with greater vasodilating properties increases perfusion of the local site with blood. The injected local anesthetic is absorbed into the cardiovascular compartment more rapidly and is carried away from the injection site and from the nerve, thus providing for a shortened duration of anesthesia, as well as decreased potency of the drug. Table 1-7 summarizes the influence of various factors on local anesthetic action.
Recovery from Local Anesthetic Block

Emergence from a local anesthetic nerve block follows the same diffusion patterns as induction; however, it does so in the reverse order.

The extraneural concentration of local anesthetic is continually depleted by diffusion, dispersion, and uptake of the drug, whereas the intraneural concentration of local anesthetic remains relatively stable. The concentration gradient is reversed, the intraneural concentration exceeds the extraneural concentration, and anesthetic molecules begin to diffuse out of the nerve.

Fasciculi in the mantle begin to lose the local anesthetic much sooner than do the core bundles. Local anesthetic within the core then diffuses into the mantle, so that the first nerve fibers to entirely lose anesthesia are those centermost in the nerve. Mantle fibers remain anesthetized the longest, and core fibers the shortest, time. Recovery from anesthesia is a slower process than induction because the local anesthetic is bound to the drug receptor site in the sodium channel and therefore is released more slowly than it is absorbed.

Readministration of Local Anesthetic

Occasionally a dental procedure outlasts the duration of clinically effective pain control, and a repeat injection of local anesthetic is necessary. Usually this repeat injection immediately results in a return of profound anesthesia. On some occasions, however, the clinician may encounter greater difficulty in reestablishing adequate pain control with subsequent injections.

Recurrence of Immediate Profound Anesthesia

At the time of reinjection, the concentration of local anesthetic in the core fibers is less than that in the mantle fibers. Partially recovered core fibers still contain some local anesthetic, although not enough to provide complete anesthesia. After deposition of a new high concentration of anesthetic near the nerve, the mantle fibers are once again exposed to a concentration gradient directed inward toward the nerve; this eventually leads to an increased concentration in the core fibers. This combination of residual local anesthetic (in the nerve) and the newly deposited supply results in rapid onset of profound anesthesia and administration of a smaller volume of local anesthetic drug.
# TABLE 1-6 Chemical Structure, Physicochemical Properties, and Pharmacologic Properties of Local Anesthetic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>CHEMICAL CONFIGURATION</th>
<th>PHYSICOCHEMICAL PROPERTIES</th>
<th>PHARMACOLOGIC PROPERTIES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aromatic (lipophilic) Chain</td>
<td>Molecular Weight (base)</td>
<td>pKa (36°C)</td>
</tr>
<tr>
<td></td>
<td>Intermediate Amine (hydrophilic)</td>
<td>Lipid Solubility</td>
<td>Approx Duration</td>
</tr>
<tr>
<td>Esters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td>![Chemical Structure]</td>
<td>236</td>
<td>9.1</td>
</tr>
<tr>
<td>Chlorprocaine</td>
<td>![Chemical Structure]</td>
<td>271</td>
<td>8.7</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>![Chemical Structure]</td>
<td>264</td>
<td>8.4</td>
</tr>
<tr>
<td>Amides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>![Chemical Structure]</td>
<td>246</td>
<td>7.9</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>![Chemical Structure]</td>
<td>220</td>
<td>7.7</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>![Chemical Structure]</td>
<td>234</td>
<td>7.7</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>![Chemical Structure]</td>
<td>274</td>
<td>8.1</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>![Chemical Structure]</td>
<td>288</td>
<td>8.1</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>![Chemical Structure]</td>
<td>276</td>
<td>7.9</td>
</tr>
<tr>
<td>Articaine</td>
<td>![Chemical Structure]</td>
<td>320</td>
<td>7.8</td>
</tr>
</tbody>
</table>


NA, Not available.
TABLE 1-7 Factors Affecting Local Anesthetic Action

<table>
<thead>
<tr>
<th>Factor</th>
<th>Action Affected</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK₂</td>
<td>Onset</td>
<td>Lower pK₂ = More rapid onset of action, more RN molecules present to diffuse through nerve sheath; thus onset time is decreased</td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>Potency</td>
<td>Increased lipid solubility = Increased potency (e.g., procaine = 1; etidocaine = 140)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Duration</td>
<td>Increased protein binding allows anesthetic cations (RNH⁺) to be more firmly attached to proteins located at receptor sites; thus duration of action is increased</td>
</tr>
<tr>
<td>Nonnervous tissue diffusibility</td>
<td>Onset</td>
<td>Increased diffusibility = Decreased time of onset</td>
</tr>
<tr>
<td>Vasodilator activity</td>
<td>Anesthetic potency and duration</td>
<td>Greater vasodilator activity = Increased blood flow to region = Rapid removal of anesthetic molecules from injection site; thus anesthetic potency and duration are decreased</td>
</tr>
</tbody>
</table>

From Cohen S, Burns RC: Pathways of the pulp, ed 6, St Louis, 1994, Mosby.

Difficulty Reaching Profound Anesthesia

In this second situation, as in the first, the dental procedure has outlasted the clinical effectiveness of the local anesthetic drug, and the patient is experiencing pain. The doctor readministers a volume of local anesthetic, but unlike in the first scenario, effective control of pain does not occur.

Tachyphylaxis

In this second clinical situation, a process known as tachyphylaxis occurs. Tachyphylaxis is defined as increasing tolerance to a drug that is administered repeatedly. It is much more likely to develop if nerve function is allowed to return before reinjection (e.g., if the patient complains of pain). The duration, intensity, and spread of anesthesia with reinjection are greatly reduced.⁴¹

Although difficult to explain, tachyphylaxis is probably brought about by some or all of the following factors: edema, localized hemorrhage, clot formation, transudation, hypernatremia, and decreased pH of tissues. The first four factors isolate the nerve from contact with the local anesthetic solution. The fifth, hypernatremia, raises the sodium ion gradient, thus counteracting the decrease in sodium ion conduction brought about by the local anesthetic. The last factor, a decrease in pH of the tissues, is brought about by the first injection of the acidic local anesthetic. The ambient pH in the area of injection may be somewhat lower, so that fewer local anesthetic molecules are transformed into the free base (RN) on reinjection.

Duration of Anesthesia

As the local anesthetic is removed from the nerve, the function of the nerve returns rapidly at first, but then it gradually slows. Compared with onset of the nerve block, which is rapid, recovery from the nerve block is much slower because the local anesthetic is bound to the nerve membrane. Longer-acting local
anesthetics (e.g., bupivacaine, etidocaine, ropivacaine, tetracaine) are more firmly bound in the nerve membrane (increased protein binding) than are shorter-acting drugs (e.g., procaine, lidocaine) and therefore are released more slowly from receptor sites in the sodium channels. The rate at which an anesthetic is removed from a nerve has an effect on the duration of neural blockade; in addition to increased protein binding, other factors that influence the rate of removal of a drug from the injection site are the vascularity of the injection site and the presence or absence of a vasoactive substance. Anesthetic duration is increased in areas of decreased vascularity (e.g., Gow-Gates mandibular nerve block vs. inferior alveolar nerve block), and the addition of a vasopressor decreases tissue perfusion to a local area, thus increasing the duration of the block.

References

<p>| | |</p>
<table>
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<tbody>
<tr>
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</tr>
</tbody>
</table>
Chapter 2 Pharmacology of Local Anesthetics

Local anesthetics, when used for the management of pain, differ from most other drugs commonly used in medicine and dentistry in one important manner. Virtually all other drugs, regardless of the route through which they are administered, must ultimately enter into the circulatory system in sufficiently high concentrations (e.g., attain therapeutic blood levels in their target organ[s]) before they can begin to exert a clinical action. Local anesthetics, however, when used for pain control, cease to provide a clinical effect when they are absorbed from the site of administration into the circulation. One prime factor involved in the termination of action of local anesthetics used for pain control is their redistribution from the nerve fiber into the cardiovascular system.

The presence of a local anesthetic in the circulatory system means that the drug will be transported to every part of the body. Local anesthetics have the ability to alter the functioning of some of these cells. In this chapter, the actions of local anesthetics, other than their ability to block conduction in nerve axons of the peripheral nervous system, are reviewed. A classification of local anesthetics is shown in Box 2-1.

Pharmacokinetics of Local Anesthetics

Uptake

When injected into soft tissues, local anesthetics exert pharmacologic action on blood vessels in the area. All local anesthetics possess a degree of vasoactivity, most producing dilation of the vascular bed into which they are deposited, although the degree of vasodilation may vary, and some may produce vasoconstriction. To some degree, these effects may be concentration dependent. Relative vasodilating values of amide local anesthetics are shown in Table 2-1. Ester local anesthetics are also potent vasodilating drugs. Procaine, the most potent vasodilator among local anesthetics, is occasionally injected clinically to induce vasodilation when peripheral blood flow has been compromised because of (accidental) intra-arterial (IA) injection of a drug (e.g., thiopental) or injection of epinephrine or norepinephrine into a fingertip or toe. IA administration of an irritating drug such as thiopental may produce arteriospasm with an attendant decrease in tissue perfusion that if prolonged could lead to tissue death, gangrene, and loss of the affected limb. In this situation, procaine is administered IA in an attempt to break the arteriospasm and reestablish blood flow to the affected limb. Tetracaine, chloroprocaine, and propoxycaine also possess vasodilating properties to varying degrees but not to the degree of procaine.

Cocaine is the only local anesthetic that consistently produces vasoconstriction. The initial action of cocaine is vasodilation followed by an intense and prolonged vasoconstriction. It is produced by inhibition of the uptake of catecholamines (especially norepinephrine) into tissue binding sites. This results in an excess of free norepinephrine, leading to a prolonged and intense state of vasoconstriction. This inhibition of the reuptake of norepinephrine has not been demonstrated with other local anesthetics, such as lidocaine and bupivacaine.

A significant clinical effect of vasodilation is an increase in the rate of absorption of the local anesthetic into the blood, thus decreasing the duration and quality (e.g., depth) of pain control, while increasing the...
anesthetic blood (or plasma) concentration and its potential for overdose (toxic reaction). The rates at which local anesthetics are absorbed into the bloodstream and reach their peak blood level vary according to the route of administration (Table 2-2).

**Oral Route**

With the exception of cocaine, local anesthetics are absorbed poorly, if at all, from the gastrointestinal tract after oral administration. In addition, most local anesthetics (especially lidocaine) undergo a significant hepatic first-pass effect after oral administration. After absorption of lidocaine from the gastrointestinal tract into the enterohepatic circulation, a fraction of the drug dose is carried to the liver, where approximately 72% of the dose is biotransformed into inactive metabolites. This has seriously hampered the use of lidocaine as an oral antidysrhythmic drug. In 1984, Astra Pharmaceuticals and Merck Sharp & Dohme introduced an analog of lidocaine, tocainide hydrochloride, which is effective orally. The chemical structures of tocainide and lidocaine are presented in Figure 2-1.

---

**Box 2-1 Classification of Local Anesthetics**

- **Esters**
  - **Esters of benzoic acid**
    - Butacaine
    - Cocaine
    - Ethyl aminobenzoate (benzocaine)
    - Hexylcaine
    - Piperocaine
    - Tetracaine
  - **Esters of para-aminobenzoic acid**
    - Chloroprocaine
    - Procaine
    - Propoxycaine
## Amides

- Articaine
- Bupivacaine
- Dibucaine
- Etidocaine
- Lidocaine
- Mepivacaine
- Prilocaine
- Ropivacaine

## Quinoline

- Centbucridine

### TABLE 2-1 Relative Vasodilating Values of Amide-Type Local Anesthetics

<table>
<thead>
<tr>
<th></th>
<th>Vasodilating Activity</th>
<th>MEAN % INCREASE IN FEMORAL ARTERY BLOOD FLOW IN DOGS AFTER INTRA-ARTERIAL INJECTION*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine</td>
<td>1 (approx)</td>
<td>5.6</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>2.5</td>
<td>45.4</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>2.5</td>
<td>44.3</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1</td>
<td>25.8</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>0.8</td>
<td>35.7</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>0.5</td>
<td>42.1</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>NA</td>
<td>37.6</td>
</tr>
</tbody>
</table>

*Each agent injected rapidly at a dose of 1 mg/0.1 mL saline.


NA, Not available.
Topical Route

Local anesthetics are absorbed at differing rates after application to mucous membrane: In the tracheal mucosa, absorption is almost as rapid as with intravenous (IV) administration (indeed, intratracheal drug administration [epinephrine, lidocaine, atropine, naloxone, and flumazenil] is used in certain emergency situations); in the pharyngeal mucosa, absorption is slower; and in the esophageal or bladder mucosa, uptake is even slower than occurs through the pharynx. Wherever no layer of intact skin is present, topically applied local anesthetics can produce an anesthetic effect. Sunburn remedies (e.g., Solarcaine, Schering-Plough HealthCare Products, Inc., Memphis, Tenn) usually contain lidocaine, benzocaine, or other anesthetics in an ointment formulation. Applied to intact skin, they do not provide an anesthetic action, but with skin damaged by sunburn, they bring rapid relief of pain. A eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA) has been developed that is able to provide surface anesthesia of intact skin.7

Figure 2-1 Tocainide. A, Represents a modification of lidocaine (B) that is able to pass through the liver after oral administration with minimal hepatic first-pass effect.

![Chemical Structure of Tocainide]

A

![Chemical Structure of Lidocaine]

B

esophageal or bladder mucosa, uptake is even slower than occurs through the pharynx. Wherever no layer of intact skin is present, topically applied local anesthetics can produce an anesthetic effect. Sunburn remedies (e.g., Solarcaine, Schering-Plough HealthCare Products, Inc., Memphis, Tenn) usually contain lidocaine, benzocaine, or other anesthetics in an ointment formulation. Applied to intact skin, they do not provide an anesthetic action, but with skin damaged by sunburn, they bring rapid relief of pain. A eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA) has been developed that is able to provide surface anesthesia of intact skin.7
### TABLE 2-2 Time to Achieve Peak Blood Level

<table>
<thead>
<tr>
<th>Route</th>
<th>Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>1</td>
</tr>
<tr>
<td>Topical</td>
<td>5 (approximately)</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>5-10</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>30-90</td>
</tr>
</tbody>
</table>

**Injection**

The rate of uptake (absorption) of local anesthetics after parenteral administration (subcutaneous, intramuscular, or IV) is related to both the vascularity of the injection site and the vasoactivity of the drug.

IV administration of local anesthetics provides the most rapid elevation of blood levels and is used clinically in the primary management of ventricular dysrhythmias. Rapid IV administration can lead to significantly high local anesthetic blood levels, which can induce serious toxic reactions. The benefits to be accrued from IV drug administration must always be carefully weighed against any risks associated with IV administration. Only when the benefits clearly outweigh the risks should the drug be administered, as is the case with pre-fatal ventricular dysrhythmias such as premature ventricular contractions (PVCs).

**Distribution**

Once absorbed into the blood, local anesthetics are distributed throughout the body to all tissues. Highly perfused organs (and areas), such as the brain, head, liver, kidneys, lungs, and spleen, initially will have higher anesthetic blood levels than less highly perfused organs. Skeletal muscle, although not as highly perfused as these areas, contains the greatest percentage of local anesthetic of any tissue or organ in the body because it constitutes the largest mass of tissue in the body.

The plasma concentration of a local anesthetic in certain target organs has a significant bearing on the potential toxicity of the drug. The blood level of the local anesthetic is influenced by the following factors:

1. Rate at which the drug is absorbed into the cardiovascular system
2. Rate of distribution of the drug from the vascular compartment to the tissues (more rapid in healthy patients than in those who are medically compromised [e.g., congestive heart failure], thus leading to lower blood levels in healthier patients)
3. Elimination of the drug through metabolic or excretory pathways

The latter two factors serve to decrease the blood level of the local anesthetic.

The rate at which a local anesthetic is removed from the blood is described as its *elimination half-life*. Simply stated, the elimination half-life is the time necessary for a 50% reduction in the blood level (one half-life = 50% reduction; two half-lives = 75% reduction; three half-lives = 87.5% reduction; four half-lives = 94% reduction; five half-lives = 97% reduction; six half-lives = 98.5% reduction) (Table 2-4).
All local anesthetics readily cross the blood–brain barrier. They also readily cross the placenta and enter the circulatory system of the developing fetus.

**Metabolism (Biotransformation, Detoxification)**

A significant difference between the two major groups of local anesthetics, the esters and the amides, is the means by which the body biologically transforms the active drug into one that is pharmacologically inactive. Metabolism (or biotransformation or detoxification) of local anesthetics is important because the overall toxicity of a drug depends on a balance between its rate of absorption into the bloodstream at the site of injection and its rate of removal from

![Figure 2-2 Pattern of distribution of local anesthetics after absorption.](Redrawn from Wildsmith JAW, Armitage EN, McClure JH: Principles and practice of regional anesthesia, ed 3, Edinburgh, 2003, Churchill Livingstone.)
Figure 2-3 Metabolic hydrolysis of procaine. \textit{PsChE}, Pseudocholinesterase.

(From Tucker GT: Biotransformation and toxicity of local anesthetics, Acta Anaesthesiol Belg 26[Suppl]: 123, 1975.)

the blood through the processes of tissue uptake and metabolism.
TABLE 2-3 Percentages of Cardiac Output Distributed to Different Organ Systems

<table>
<thead>
<tr>
<th>Region</th>
<th>Percent of Cardiac Output Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>22</td>
</tr>
<tr>
<td>Gastrointestinal system, spleen</td>
<td>21</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>15</td>
</tr>
<tr>
<td>Brain</td>
<td>14</td>
</tr>
<tr>
<td>Skin</td>
<td>6</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
</tr>
<tr>
<td>Heart muscle</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
</tbody>
</table>


TABLE 2-4 Half-Life of Local Anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life, hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine*</td>
<td>0.1</td>
</tr>
<tr>
<td>Procaine*</td>
<td>0.1</td>
</tr>
<tr>
<td>Tetracaine*</td>
<td>0.3</td>
</tr>
<tr>
<td>Articaine†</td>
<td>0.5</td>
</tr>
<tr>
<td>Cocaine*</td>
<td>0.7</td>
</tr>
<tr>
<td>Prilocaine†</td>
<td>1.6</td>
</tr>
<tr>
<td>Lidocaine†</td>
<td>1.6</td>
</tr>
<tr>
<td>Mepivacaine†</td>
<td>1.9</td>
</tr>
<tr>
<td>Ropivacaine†</td>
<td>1.9</td>
</tr>
<tr>
<td>Etidocaine†</td>
<td>2.6</td>
</tr>
<tr>
<td>Bupivacaine†</td>
<td>3.5</td>
</tr>
<tr>
<td>Propoxycaine*</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Ester.
† Amide.

TABLE 2-5 Hydrolysis Rate of Esters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate of Hydrolysis, µmol/mL/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine</td>
<td>4.7</td>
</tr>
<tr>
<td>Procaine</td>
<td>1.1</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Ester Local Anesthetics

Ester local anesthetics are hydrolyzed in the plasma by the enzyme pseudocholinesterase.\textsuperscript{10} The rate at which hydrolysis of different esters occurs varies considerably (Table 2-5).
The rate of hydrolysis has an impact on the potential toxicity* of a local anesthetic. Chloroprocaine, the most rapidly hydrolyzed, is the least toxic, whereas tetracaine, hydrolyzed 16 times more slowly than chloroprocaine, has the greatest potential toxicity. Procaine undergoes hydrolysis to para-aminobenzoic acid (PABA), which is excreted unchanged in the urine, and to diethylamine alcohol, which undergoes further biotransformation before excretion (Fig. 2-3). Allergic reactions that occur in response to ester local anesthetics usually are not related to the parent compound (e.g., procaine) but rather to PABA, which is a major metabolic product of many ester local anesthetics.

Approximately 1 of every 2800 persons has an atypical form of pseudocholinesterase, which causes an inability to hydrolyze ester local anesthetics and other chemically related drugs (e.g., succinylcholine). Its presence leads to prolongation of higher local anesthetic blood levels and increased potential for toxicity.

Succinylcholine is a short-acting muscle relaxant commonly employed during the induction phase of general anesthesia. It produces respiratory arrest (apnea) for a period of approximately 2 to 3 minutes. Then plasma pseudocholinesterase hydrolyzes succinylcholine, blood levels fall, and spontaneous respiration resumes. Persons with atypical pseudocholinesterase are unable to hydrolyze succinylcholine at a normal rate; therefore the duration of apnea is prolonged. Atypical pseudocholinesterase is a hereditary trait. Any familial history of difficulty during general anesthesia should be carefully evaluated by the doctor before dental care commences. A confirmed or strongly suspected history, in the patient or biological family, of atypical pseudocholinesterase represents a relative contraindication to administration of ester-type local anesthetics.

There are absolute and relative contraindications to the administration of drugs. An absolute contraindication implies that under no circumstance should the drug in question be administered to this patient because the possibility of potentially toxic or lethal reactions is increased, whereas a relative contraindication means that the drug in question may be administered to the patient after careful weighing of the risk associated with use of the drug versus the potential benefit to be gained, and if an acceptable alternative drug is not available. However, the smallest clinically effective dose always should be used because the likelihood of adverse reaction to this drug is increased in this patient.

* ALL chemicals (drugs) have the potential to be poisons, also called toxins. When the resulting blood level is too high, drugs exert negative actions, which we call a toxic reaction or overdose.

Amide Local Anesthetics

The biotransformation of amide local anesthetics is more complex than that of the esters. The primary site of biotransformation of amide local anesthetics is the liver. Virtually the entire metabolic process occurs in the liver for lidocaine, mepivacaine, etidocaine, and bupivacaine. Prilocaine undergoes primary metabolism in the liver, with some also possibly occurring in the lung. Articaine, a hybrid molecule containing both ester and amide components, undergoes metabolism in both the blood and the liver.

The rates of biotransformation of lidocaine, mepivacaine, etidocaine, and bupivacaine are similar. Therefore liver function and hepatic perfusion significantly influence the rate of biotransformation of an amide local anesthetic. Approximately 70% of a dose of injected lidocaine undergoes biotransformation...
in patients with normal liver function. Patients with lower than usual hepatic blood flow (hypotension, congestive heart failure) or poor liver function (cirrhosis) are unable to biotransform amide local anesthetics at a normal rate. This slower than normal biotransformation rate results in higher anesthetic blood levels and increased risk of toxicity. Significant liver dysfunction (American Society of Anesthesiologists Physical Status classification system [ASA] 4 to 5) or heart failure (ASA 4 to 5) represents a relative contraindication to the administration of amide local anesthetic drugs (Table 2-6). Articaine has a shorter half-life than other amides (27 minutes vs. 90 minutes) because a portion of its biotransformation occurs in the blood by the enzyme plasma cholinesterase.17

The biotransformation products of certain local anesthetics can possess significant clinical activity if they are permitted to accumulate in the blood. This may be seen in renal or cardiac failure and during periods of prolonged drug administration. A clinical example is the production of methemoglobinemia in patients receiving large doses of prilocaine. Prilocaine, the parent compound, does not produce methemoglobinemia, but orthotoluidine, a primary metabolite of prilocaine, does induce the formation of methemoglobin, which is responsible for methemoglobinemia. When methemoglobin blood levels become elevated, clinical signs and symptoms are observed. Methemoglobinemia is discussed more fully in Chapter 10. Another example of pharmacologically active metabolites is the sedative effect occasionally observed after lidocaine administration. Lidocaine does not produce sedation; however, two metabolites—monoethylglycinexylidide and glycine xylidide—are thought to be responsible for this clinical action.20

The metabolic pathways of lidocaine and prilocaine are shown in Figures 2-4 and 2-5.

### TABLE 2-6 Lidocaine Disposition in Various Groups of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Lidocaine Half-Life, hr</th>
<th>Mean Total Body Clearance, mL/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.8</td>
<td>10</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>4.9</td>
<td>6</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.3</td>
<td>13.7</td>
</tr>
</tbody>
</table>


[Development of Local Anesthetic Agents: Timeline]

**ESTERS**

<table>
<thead>
<tr>
<th>cocaine</th>
<th>procaine</th>
<th>tetracaine</th>
<th>chloroprocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>1884</td>
<td>1905</td>
<td>1922</td>
<td>1938</td>
</tr>
</tbody>
</table>

**AMIDES**

<table>
<thead>
<tr>
<th>dibucaine</th>
<th>lidocaine</th>
<th>meptacaine</th>
<th>prilocaine</th>
<th>bupivacaine</th>
<th>etidocaine</th>
<th>articaine</th>
<th>ropivacaine</th>
<th>levobupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Excretion

The kidneys are the primary excretory organ for both the local anesthetic and its metabolites. A percentage of a given dose of local anesthetic is excreted unchanged in the urine. This percentage varies according to the drug. Esters appear only in very small concentrations as the parent compound in the urine because they are hydrolyzed almost completely in the plasma. Procaine appears in the urine as PABA (90%) with 2% unchanged. Ten percent of a cocaine dose is found in the urine unchanged. Amides usually are present in the urine as the parent compound in a greater percentage than the esters, primarily because of their more complex process of biotransformation. Although the percentages of parent drug found in urine vary from study to study, less than 3% lidocaine, 1% mepivacaine, and 1% etidocaine is found unchanged in the urine.

Patients with significant renal impairment may be unable to eliminate the parent local anesthetic compound or its major metabolites from the blood, resulting in slightly elevated blood levels and therefore increased potential for toxicity. This may occur with the esters or amides and is especially likely with cocaine. Thus significant renal disease (ASA 4 to 5) represents a relative contraindication to the administration of local anesthetics. This includes patients undergoing renal dialysis and those with chronic glomerulonephritis or pyelonephritis.

Systemic Actions of Local Anesthetics

Local anesthetics are chemicals that reversibly block action potentials in all excitable membranes. The central nervous system (CNS) and the cardiovascular system (CVS) therefore are especially susceptible to their actions. Most of the systemic actions of local anesthetics are related to their blood or plasma level in the target organ (CNS, CVS). The higher the level, the greater will be the clinical action.

Centbucridine (a quinoline derivative) has proved to be five to eight times as potent a local anesthetic as lidocaine, with an equally rapid onset of action and an equivalent duration. Of potentially great importance is the finding that it does not adversely affect the CNS or CVS, except in very high doses.
Figure 2-4 Metabolic pathways of lidocaine. Percentages of dose found in urine are indicated in parentheses.

(From Kennaghan JB, Boyes RN: The tissue distribution, metabolism, and excretion of lidocaine in rats, guinea pigs, dogs and man, J Pharmacol Exp Ther Feb 180(2):454–463, 1972.)
Local anesthetics are absorbed from their site of administration into the circulatory system, which effectively dilutes them and carries them to all cells of the body. The ensuing blood level of the local anesthetic depends on its rate of uptake from the site of administration into the circulatory system (increasing the blood level), and on the rates of distribution in tissue and biotransformation (in the liver), processes that remove the drug from the blood (decreasing the blood level) (see \textbf{Fig. 2-2}).

**Central Nervous System**

Local anesthetics readily cross the blood–brain barrier. Their pharmacologic action on the CNS is seen as depression. At low (therapeutic, nontoxic) blood levels, no CNS effects of any clinical significance have been noted. At higher (toxic, overdose) levels, the primary clinical manifestation is a generalized tonic–clonic convulsion. Between these two extremes exists a spectrum of other clinical signs and symptoms. (See \textbf{Box 2-2}, “Preconvulsive Signs and Symptoms of Central Nervous Toxicity.”)

**Anticonvulsant Properties**

Some local anesthetics (e.g., procaine, lidocaine, mepivacaine, prilocaine, even cocaine) have demonstrated anticonvulsant properties.\textsuperscript{23,24} These occur at a blood level considerably below that at which the same drugs produce seizure activity. Values for anticonvulsive blood levels of lidocaine are shown in \textbf{Table 2-7}.\textsuperscript{25}

Procaine, mepivacaine, and lidocaine have been used intravenously to terminate or decrease the duration of both grand mal and petit mal seizures.\textsuperscript{23,26} The anticonvulsant blood level of lidocaine (about 0.5 to 4 µg/mL) is very close to its cardiotherapeutic range (see following). It has been demonstrated to be effective in temporarily arresting seizure activity in a majority of human epileptic patients.\textsuperscript{27} It was especially effective in interrupting status epilepticus
Figure 2-5 Metabolic pathways of prilocaine. Percentages of dose found in urine are indicated in parentheses.
at therapeutic doses of 2 to 3 mg/kg when given at a rate of 40 to 50 mg/min.

**Box 2-2 Preconvulsive Signs and Symptoms of Central Nervous System Toxicity**

<table>
<thead>
<tr>
<th>Signs (objectively observable)</th>
<th>Symptoms (subjectively felt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slurred speech</td>
<td>Numbness of tongue and circumoral region</td>
</tr>
<tr>
<td>Shivering</td>
<td>Warm, flushed feeling of skin</td>
</tr>
<tr>
<td>Muscular twitching</td>
<td>Pleasant dreamlike state</td>
</tr>
<tr>
<td>Tremor of muscles of face and distal extremities</td>
<td></td>
</tr>
<tr>
<td>Generalized lightheadedness</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Visual disturbances (inability to focus)</td>
<td></td>
</tr>
<tr>
<td>Auditory disturbance (tinnitus)</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
</tr>
<tr>
<td>Disorientation</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2-7 Anticonvulsive Blood Levels of Lidocaine**

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Lidocaine Blood Level, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsive level</td>
<td>0.5-4</td>
</tr>
<tr>
<td>Preseizure signs and symptoms</td>
<td>4.5-7</td>
</tr>
<tr>
<td>Tonic–clonic seizure</td>
<td>&gt;7.5</td>
</tr>
</tbody>
</table>

**Mechanism of Anticonvulsant Properties**

Epileptic patients possess hyperexcitable cortical neurons at a site within the brain where the convulsive episode originates (called the *epileptic focus*). Local anesthetics, by virtue of their depressant actions on the CNS, raise the seizure threshold by decreasing the excitability of these neurons, thereby preventing or terminating seizures.

**Preconvulsive Signs and Symptoms**

With a further increase in the blood level of the local anesthetic to above its therapeutic level, adverse reactions may be observed. Because the CNS is much more susceptible than other systems to the actions of local anesthetics, it is not surprising that the initial clinical signs and symptoms of overdose (toxicity) are CNS in origin. With lidocaine, this second phase is observed at a level between 4.5 and 7 µg/mL in the average normal healthy patient. Initial clinical signs and symptoms of CNS toxicity are usually excitatory in nature (see Box 2-2).
All of these signs and symptoms, except for the sensation of circumoral and lingual numbness, are related to the direct depressant action of the local anesthetic on the CNS. Numbness of the tongue and circumoral regions is not caused by CNS effects of the local anesthetic. Rather it is the result of a direct anesthetic action of the local anesthetic, which is present in high concentrations in these highly vascular tissues, on free nerve endings. The anesthetic has been transported to these tissues by the CVS. A dentist treating a patient might have difficulty conceptualizing why anesthesia of the tongue is considered to be a sign of a toxic reaction when lingual anesthesia is commonly produced after mandibular nerve blocks. Consider for a moment a physician administering a local anesthetic into the patient's foot. Overly high blood levels would produce bilateral numbing of the tongue, as contrasted with the usual unilateral anesthesia seen after dental nerve blocks.

Lidocaine and procaine differ somewhat from other local anesthetics in that the usual progression of signs and symptoms just noted may not be seen. Lidocaine and procaine frequently produce an initial mild sedation or drowsiness (more common with lidocaine). Because of this potential, the U.S. Air Force and the U.S. Navy ground airplane pilots for 24 hours after receipt of a local anesthetic.

Sedation may develop in place of the excitatory signs. If excitation or sedation is observed during the first 5 to 10 minutes after intraoral administration of a local anesthetic, it should serve as a warning to the clinician of a rising local anesthetic blood level and the possibility (if the blood level continues to rise) of a more serious reaction, including a generalized convulsive episode.

* Individual variation in response to drugs, as depicted in the normal distribution curve, may produce clinical symptoms at levels lower than these (in hyperresponders) or may fail to produce them at higher levels (in hyporesponders).

**Convulsive Phase**

Further elevation of the local anesthetic blood level leads to signs and symptoms consistent with a generalized tonic–clonic convulsive episode. The duration of seizure activity is related to the local anesthetic blood level and is inversely related to the arterial partial pressure of carbon dioxide (pCO₂) level. At a normal pCO₂, a lidocaine blood level between 7.5 and 10 µg/mL usually results in a convulsive episode. When carbon dioxide (CO₂) levels are increased, the blood level of local anesthetic necessary for seizures decreases while the duration of the seizure increases. Seizure activity generally is self-limiting, because cardiovascular activity usually is not significantly impaired, and redistribution and biotransformation of the local anesthetic continue throughout the episode. This results in a decrease in anesthetic blood level and termination of seizure activity, usually within 1 minute.

However, several other mechanisms also at work unfortunately act to prolong the convulsive episode. Both cerebral blood flow and cerebral metabolism are increased during local anesthetic-induced convulsions. Increased blood flow to the brain leads to an increase in the volume of local anesthetic being delivered to the brain, tending to prolong the seizure. Increased cerebral metabolism leads to a progressive metabolic acidosis as the seizure continues, and this tends to prolong the seizure activity (by lowering the blood level of anesthetic necessary to provoke a seizure), even in the presence of a declining
local anesthetic level in the blood. As noted in Tables 2-8 and 2-9, the dose of local anesthetic necessary to induce seizures is markedly diminished in the presence of hypercarbia (see Table 2-8) or acidosis (see Table 2-9). 31,32

Further increases in local anesthetic blood level result in cessation of seizure activity as electroencephalographic (EEG) tracings become flattened, indicative of a generalized CNS depression. Respiratory depression occurs at this time, eventually leading to respiratory arrest if anesthetic blood levels continue to rise. Respiratory effects are a result of the depressant action of the local anesthetic drug on the CNS.

**Mechanism of Preconvulsant and Convulsant Actions**

It is known that local anesthetics exert a depressant action on excitable membranes, yet the primary clinical manifestation associated with high local anesthetic blood levels is related to varying degrees of stimulation. How can a drug that depresses the CNS be responsible for the production of varying degrees of stimulation, including tonic–clonic seizure activity? It is thought that local anesthetics produce clinical signs and symptoms of CNS excitation (including convulsions) through selective blockade of inhibitory pathways in the cerebral cortex. 32-35 de Jong states that “inhibition of inhibition thus is a presynaptic event that follows local anesthetic blockade of impulses traveling along inhibitory pathways.”

**TABLE 2-8** Effects of pCO₂ on the Convulsive Threshold (CD₁₀₀) of Various Local Anesthetics in Cats

<table>
<thead>
<tr>
<th>Agent</th>
<th>pCO₂ (25-40 torr)</th>
<th>pCO₂ (6581 torr)</th>
<th>Percent Change in CD₁₀₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td>35</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>18</td>
<td>10</td>
<td>44</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>22</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>15</td>
<td>7</td>
<td>53</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>5</td>
<td>2.5</td>
<td>50</td>
</tr>
</tbody>
</table>


**TABLE 2-9** Convulsant Dose (CD₁₀₀) and Acid-Base Status*

<table>
<thead>
<tr>
<th></th>
<th>pH 7.10</th>
<th>pH 7.20</th>
<th>pH 7.30</th>
<th>pH 7.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCO₂ 30</td>
<td>—</td>
<td>—</td>
<td>27.5</td>
<td>26.6</td>
</tr>
<tr>
<td>pCO₂ 40</td>
<td>—</td>
<td>20.6</td>
<td>21.4</td>
<td>22.0</td>
</tr>
<tr>
<td>pCO₂ 60</td>
<td>13.1</td>
<td>15.4</td>
<td>17.5</td>
<td>—</td>
</tr>
<tr>
<td>pCO₂ 80</td>
<td>11.3</td>
<td>14.3</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>


* Intravenous lidocaine 5 mg/kg/min, cats; doses in mg/kg.
The cerebral cortex has pathways of neurons that are essentially inhibitory and others that are facilitatory (excitatory). A state of balance normally is maintained between the degrees of effect exerted by these neuronal paths (Fig. 2-6). At preconvulsant local anesthetic blood levels, observed clinical signs and symptoms are produced because the local anesthetic selectively depresses the action of inhibitory neurons (Fig. 2-7). Balance then is tipped slightly in favor of excessive facilitatory (excitatory) input, leading to symptoms of tremor and slight agitation.

At higher (convulsive) blood levels, inhibitory neuron function is completely depressed, allowing unopposed function of facilitatory neurons (Fig. 2-8). Pure facilitatory input without inhibition produces the tonic–clonic activity observed at these levels.

Further increases in anesthetic blood level lead to depression of the facilitatory and inhibitory pathways, producing generalized CNS depression (Fig. 2-9). The precise site of action of the local anesthetic within the CNS is not known but is thought to be at the inhibitory cortical synapses or directly on the inhibitory cortical neurons.

Figure 2-6 Balance between inhibitory and facilitatory impulses in a normal cerebral cortex.
Figure 2-7 In the preconvulsive stage of local anesthetic action, the inhibitory impulse is more profoundly depressed than the facilitatory impulse.

Analgesia

Local anesthetics possess a second action in relation to the CNS. Administered intravenously, they increase the pain reaction threshold and also produce a degree of analgesia.

In the 1940s and 1950s, procaine was administered intravenously for the management of chronic pain and arthritis. The “procaine unit” was commonly used for this purpose; it consisted of 4 mg/kg of body weight administered over 20 minutes. The technique was ineffective for acute pain. Because of the relatively narrow safety margin between the analgesic actions of procaine and the occurrence of signs and symptoms of overdose, this technique is no longer in use today.
Mood Elevation

The use of local anesthetic drugs for mood elevation and rejuvenation has persisted for centuries,

Figure 2-8 In the convulsive stage of local anesthetic action, the inhibitory impulse is totally depressed, permitting unopposed facilitatory impulse activity.
Despite documentation of both catastrophic events (mood elevation) and lack of effect (rejuvenation).

Cocaine has long been used for its euphoria-inducing and fatigue-lessening actions, dating back to the chewing of coca leaves by Incas and other South American natives.\textsuperscript{38,39} Unfortunately, as is well documented today, prolonged use of cocaine leads to habituation. William Stewart Halsted (1852-1922), the father of American surgery, cocaine researcher, and the first person to administer a local anesthetic by injection, suffered greatly because of an addiction to cocaine.\textsuperscript{40} In more recent times, the sudden, unexpected deaths of several prominent professional athletes caused by cocaine and the addiction of many others clearly demonstrate the dangers involved in the casual use of potent drugs.\textsuperscript{41,42}

More benign, but totally unsubstantiated, is the use of procaine (Novocain) as a rejuvenating drug. Clinics professing to “restore youthful vigor” claim that procaine is a literal Fountain of Youth. These clinics operate primarily in central Europe and Mexico, where procaine is used under the proprietary
name Gerovital. de Jong states that “whatever the retarding effect on aging, it probably is relegated most charitably to mood elevation.”

**TABLE 2-10 Intravenous Dose of Local Anesthetic Agents Required for Convulsive Activity (CD<sub>100</sub>) and Irreversible Cardiovascular Collapse (LD<sub>100</sub>) in Dogs**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CD&lt;sub&gt;100&lt;/sub&gt;, mg/kg</th>
<th>LD&lt;sub&gt;100&lt;/sub&gt;, mg/kg</th>
<th>LD&lt;sub&gt;100&lt;/sub&gt;/CD&lt;sub&gt;100&lt;/sub&gt; Agent Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>22</td>
<td>76</td>
<td>3.5</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>8</td>
<td>40</td>
<td>5.0</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>4</td>
<td>20</td>
<td>5.0</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>5</td>
<td>27</td>
<td>5.4</td>
</tr>
</tbody>
</table>


**Cardiovascular System**

Local anesthetics have a direct action on the myocardium and peripheral vasculature. In general, however, the cardiovascular system appears to be more resistant than the CNS to the effects of local anesthetic drugs (Table 2-10).

**Direct Action on the Myocardium**

Local anesthetics modify electrophysiologic events in the myocardium in a manner similar to their actions on peripheral nerves. As the local anesthetic blood level increases, the rate of rise of various phases of myocardial depolarization is reduced. No significant change in resting membrane potential occurs, and no significant prolongation of the phases of repolarization is seen.

Local anesthetics produce a myocardial depression that is related to the local anesthetic blood level. Local anesthetics decrease the electrical excitability of the myocardium, decrease the conduction rate, and decrease the force of contraction.

Therapeutic advantage is taken of this depressant action in managing the hyperexcitable myocardium, which manifests as various cardiac dysrhythmias. Although many local anesthetics have demonstrated antidysrhythmic actions in animals, only procaine and lidocaine have gained significant clinical reliability in humans. Lidocaine is the most widely used and intensively studied local anesthetic in this regard. Procainamide is the procaine molecule with an amide linkage replacing the ester linkage. Because of this, it is hydrolyzed much more slowly than procaine. Tocainide, a chemical analog of lidocaine, was introduced in 1984 as an oral antidysrhythmic drug, because lidocaine is ineffective after oral administration. Tocainide also is effective in managing ventricular dysrhythmias but is associated with a 40% incidence of adverse effects, including nausea, vomiting, tremor, paresthesias, agranulocytosis, and pulmonary fibrosis. Tocainide worsens symptoms of congestive
Heart failure in about 5% of patients and may provoke dysrhythmias (i.e., is prodysrhythmic) in 1% to 8%.  

Blood levels of lidocaine usually noted after intraoral injection of one or two dental cartridges, 0.5 to 2 µg/mL, are not associated with cardiodepressant activity. Increasing lidocaine blood levels slightly is nontoxic and is associated with antidysrhythmic actions. Therapeutic blood levels of lidocaine for antidysrhythmic activity range from 1.8 to 6 µg/mL.  

Lidocaine usually is administered intravenously in a bolus of 50 to 100 mg at a rate of 25 to 50 mg/min. This dose is based on 1 to 1.5 mg/kg of body weight every 3 to 5 minutes and is frequently followed by a continuous IV infusion of 1 to 4 mg/min. Signs and symptoms of local anesthetic overdose will be noted if the blood level rises beyond 6 µg/mL of blood.  

Lidocaine is used clinically primarily in the management of PVCs and ventricular tachycardia. It also is used as a (class-indeterminate) drug in advanced cardiovascular life support and in management of cardiac arrest caused by ventricular fibrillation.  

Direct cardiac actions of local anesthetics at blood levels greater than the therapeutic (antidysrhythmic) level include a decrease in myocardial contractility and decreased cardiac output, both of which lead to circulatory collapse (see Table 2-10).  

Box 2-3 summarizes the CNS and cardiovascular effects of increasing local anesthetic blood levels.

**Direct Action on the Peripheral Vasculature**

Cocaine is the only local anesthetic drug that consistently produces vasoconstriction at commonly employed dosages. Ropivacaine causes cutaneous vasoconstriction, whereas its congener bupivacaine produces vasodilation. All other local anesthetics produce a peripheral vasodilation through relaxation of smooth muscle in the walls of blood vessels. This leads to increased blood flow to and from the site of local anesthetic deposition (see Table 2-1). Increased local blood flow increases the rate of drug absorption, in turn leading to decreased depth and duration of local anesthetic action, increased bleeding in the treatment area, and increased local anesthetic blood levels.  

Table 2-11 provides examples of peak blood levels achieved after local anesthetic injection with and without the presence of a vasopressor.  

The primary effect of local anesthetics on blood pressure is hypotension. Procaine produces hypotension more frequently and significantly than does lidocaine: 50% of patients in one study receiving procaine became hypotensive, compared with 6% of those receiving lidocaine. This action is produced by direct depression of the myocardium and smooth muscle relaxation in the vessel walls by the local anesthetic.  

In summary, negative effects on the cardiovascular system are not noted until significantly elevated local anesthetic blood levels are reached. The usual sequence of local anesthetic–induced actions on the cardiovascular system is as follows:
1 At nonoverdose levels, a slight increase or no change in blood pressure occurs because of increased cardiac output and heart rate as a result of enhanced sympathetic activity; direct vasoconstriction of certain peripheral vascular beds is also noted.

2 At levels approaching yet still below overdose, a mild degree of hypotension is noted; this is produced by a direct relaxant action on the vascular smooth muscle.

3 At overdose levels, profound hypotension is caused by decreased myocardial contractility, cardiac output, and peripheral resistance.

4 At lethal levels, cardiovascular collapse is noted. This is caused by massive peripheral vasodilation and decreased myocardial contractility and heart rate (sinus bradycardia).

5 Certain local anesthetics such as bupivacaine (and to a lesser degree ropivacaine and etidocaine) may precipitate potentially fatal ventricular fibrillation.\textsuperscript{62,63}

### Box 2-3 Minimal to Moderate Overdose Levels

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms (progressive with increasing blood levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talkativeness</td>
<td>Lightheadedness and dizziness</td>
</tr>
<tr>
<td>Apprehension</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Excitability</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>Sensation of twitching before actual twitching is observed (see “Generalized stutter” under “SIGNS”)</td>
</tr>
<tr>
<td>Generalized stutter, leading to muscular twitching and tremor in the face and distal extremities</td>
<td>Metallic taste</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Visual disturbances (inability to focus)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Auditory disturbances (tinnitus)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Drowsiness and disorientation</td>
</tr>
<tr>
<td>Sweating</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Failure to follow commands or be reasoned with</td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td></td>
</tr>
<tr>
<td>Elevated heart rate</td>
<td></td>
</tr>
<tr>
<td>Elevated respiratory rate</td>
<td></td>
</tr>
</tbody>
</table>

**Moderate to High Overdose Levels**

Tonic–clonic seizure activity followed by
Generalized central nervous system depression
Depressed blood pressure, heart rate, and respiratory rate

From Malamed SF: Medical emergencies in the dental office, ed 6, St Louis, 2007, Mosby.

<table>
<thead>
<tr>
<th>Injection Site</th>
<th>Anesthetic</th>
<th>Dose, mg</th>
<th>Epinephrine Dilution</th>
<th>Peak Level, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltration</td>
<td>Lidocaine</td>
<td>400</td>
<td>None</td>
<td>2.0</td>
</tr>
<tr>
<td>Infiltration</td>
<td>Lidocaine</td>
<td>400</td>
<td>1:200,000</td>
<td>1.0</td>
</tr>
<tr>
<td>Intercostal</td>
<td>Lidocaine</td>
<td>400</td>
<td>None</td>
<td>6.5</td>
</tr>
<tr>
<td>Intercostal</td>
<td>Lidocaine</td>
<td>400</td>
<td>1:200,000</td>
<td>5.3</td>
</tr>
<tr>
<td>Intercostal</td>
<td>Lidocaine</td>
<td>400</td>
<td>1:80,000</td>
<td>4.9</td>
</tr>
<tr>
<td>Infiltration</td>
<td>Mepivacaine</td>
<td>5 mg/kg</td>
<td>None</td>
<td>1.2</td>
</tr>
<tr>
<td>Infiltration</td>
<td>Mepivacaine</td>
<td>5 mg/kg</td>
<td>1:200,000</td>
<td>0.7</td>
</tr>
</tbody>
</table>


Local Tissue Toxicity

Skeletal muscle appears to be more sensitive than other tissues to the local irritant properties of local anesthetics. Intramuscular and intraoral injection of articaine, lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine can produce skeletal muscle alterations. It appears that longer-acting local anesthetics cause more localized skeletal muscle damage than shorter-acting drugs. The changes that occur in skeletal muscle are reversible, with muscle regeneration being complete within 2 weeks after local anesthetic administration. These muscle changes have not been associated with any overt clinical signs of local irritation.

Respiratory System

Local anesthetics exert a dual effect on respiration. At nonoverdose levels, they have a direct relaxant action on bronchial smooth muscle, whereas at overdose levels, they may produce respiratory arrest as a result of generalized CNS depression. In general, respiratory function is unaffected by local anesthetics until near-overdose levels are achieved.

Miscellaneous Actions

Neuromuscular Blockade

Many local anesthetics have been demonstrated to block neuromuscular transmission in humans. This is a result of the inhibition of sodium diffusion through a blockade of sodium channels in the cell membrane.
This action normally is slight and usually is clinically insignificant. On occasion, however, it can be additive to that produced by both depolarizing (e.g., succinylcholine) and nondepolarizing (e.g., atracurium, vecuronium) muscle relaxants; this may lead to abnormally prolonged periods of muscle paralysis. Such actions are unlikely to occur in the dental outpatient.

Drug Interactions

In general, CNS depressants (e.g., opioids, antianxiety drugs, phenothiazines, barbiturates), when administered in conjunction with local anesthetics, lead to potentiation of the CNS-depressant actions of the local anesthetic. The conjoint use of local anesthetics and drugs that share a common metabolic pathway can produce adverse reactions. Both ester local anesthetics and the depolarizing muscle relaxant succinylcholine require plasma pseudocholinesterase for hydrolysis. Prolonged apnea may result from concomitant use of these drugs.

Drugs that induce the production of hepatic microsomal enzymes (e.g., barbiturates) may alter the rate at which amide local anesthetics are metabolized. Increased hepatic microsomal enzyme induction increases the rate of metabolism of the local anesthetic.

Specific drug–drug interactions related to the administration of local anesthetics are reviewed in Chapter 10.

Malignant Hyperthermia

Malignant hyperthermia (MH; hyperpyrexia) is a pharmacogenic disorder in which a genetic variant in an individual alters that person's response to certain drugs. Acute clinical manifestations of MH include tachycardia, tachypnea, unstable blood pressure, cyanosis, respiratory and metabolic acidosis, fever (as high as 42°C [108°F] or more), muscle rigidity, and death. Mortality ranges from 63% to 73%. Many commonly used anesthetic drugs can trigger MH in certain individuals.

Until recently, the amide local anesthetics were thought to be capable of provoking MH and were considered to be absolutely contraindicated in MH-susceptible patients. The Malignant Hyperthermia Association of the United States (MHAUS), after evaluating recent clinical research, concluded that in fact no documented cases in the medical or dental literature (over the past 30 years) support the concept of amide anesthetics triggering malignant hyperthermia.

MHAUS maintains a Website with information for both health care providers and patients: www.mhaus.org.

References


23. Bernhard, CG, Bohm, E: Local anaesthetics as anticonvulsants: a study on experimental and clinical epilepsy. 1965, Almqvist & Wiksell, Stockholm.


36. de Jong, RH: Local anesthetics. 1994, Mosby, St Louis.


43. de Jong, RH: Local anesthetics. ed 2, 1977, Charles C Thomas, Springfield, Ill, p 89.


<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
</table>
Chapter 3 Pharmacology of Vasoconstrictors

All clinically effective injectable local anesthetics are vasodilators, the degree of vasodilation varying from significant (procaine) to minimal (prilocaine, mepivacaine) and also possibly with both the injection site and individual patient response. After local anesthetic injection into tissues, blood vessels (arterioles and capillaries primarily) in the area dilate, resulting in increased perfusion at the site, leading to the following reactions:

1. An increased rate of absorption of the local anesthetic into the cardiovascular system, which in turn removes it from the injection site (redistribution).
2. Higher plasma levels of the local anesthetic, with an attendant increase in the risk of local anesthetic toxicity (overdose).
3. Decrease in both the depth and duration of anesthesia because the local anesthetic diffuses away from the injection site more rapidly.
4. Increased bleeding at the site of treatment as a result of increased perfusion.

Vasoconstrictors are drugs that constrict blood vessels and thereby control tissue perfusion. They are added to local anesthetic solutions to oppose the inherent vasodilatory actions of the local anesthetics. Vasoconstrictors are important additions to a local anesthetic solution for the following reasons:

1. By constricting blood vessels, vasoconstrictors decrease blood flow (perfusion) to the site of drug administration.
2. Absorption of the local anesthetic into the cardiovascular system is slowed, resulting in lower anesthetic blood levels. Table 3-1 illustrates levels of local anesthetic in the blood with and without a vasoconstrictor.
3. Local anesthetic blood levels are lowered, thereby decreasing the risk of local anesthetic toxicity.
4. More local anesthetic enters into the nerve, where it remains for longer periods, thereby increasing (in some cases significantly, in others minimally) the duration of action of most local anesthetics.
5. Vasoconstrictors decrease bleeding at the site of administration; therefore they are useful when increased bleeding is anticipated (e.g., during a surgical procedure).

The vasoconstrictors commonly used in conjunction with injected local anesthetics are chemically identical or similar to the sympathetic nervous system mediators epinephrine and norepinephrine. The actions of the vasoconstrictors so resemble the response of adrenergic nerves to stimulation that they are classified as sympathomimetic, or adrenergic, drugs. These drugs have many clinical actions besides vasoconstriction.

Sympathomimetic drugs also may be classified according to their chemical structure and mode of action.
Chemical Structure

Classification of sympathomimetic drugs by chemical structure is related to the presence or absence of a catechol nucleus. Catechol is orthodihydroxybenzene. Sympathomimetic drugs that have hydroxyl (OH) substitutions in the third and fourth positions of the aromatic ring are termed catechols.

If they also contain an amine group (NH$_2$) attached to the aliphatic side chain, they are then called catecholamines. Epinephrine, norepinephrine, and dopamine are the naturally occurring catecholamines of the sympathetic nervous system. Isoproterenol and levonordefrin are synthetic catecholamines.

### TABLE 3-1 Effects of Vasoconstrictor (Epinephrine 1:200,000) on Peak Local Anesthetic Levels in Blood

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Dose, mg</th>
<th>PEAK LEVEL, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Vasoconstrictor</td>
<td>With Vasoconstrictor</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>500</td>
<td>4.7</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>400</td>
<td>4.3</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>400</td>
<td>2.8</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>300</td>
<td>1.4</td>
</tr>
</tbody>
</table>


Vasoconstrictors that do not possess OH groups in the third and fourth positions of the aromatic molecule are not catechols but are amines because they have an NH$_2$ group attached to the aliphatic side chain.
Felypressin, a synthetic analog of the polypeptide vasopressin (antidiuretic hormone), is available in many countries as a vasoconstrictor. As of the time of this writing (November 2011), felypressin is not available in the United States.

**Modes of Action**

Three categories of sympathomimetic amines are known: direct-acting drugs, which exert their action directly on adrenergic receptors; indirect-acting drugs, which act by releasing norepinephrine from adrenergic nerve terminals; and mixed-acting drugs, with both direct and indirect actions (Box 3-1).

**Adrenergic Receptors**

Adrenergic receptors are found in most tissues of the body. The concept of adrenergic receptors was proposed by Ahlquist in 1948 and is well accepted today. Ahlquist recognized two types of adrenergic receptor, termed alpha (α) and beta (β), based on inhibitory or excitatory actions of catecholamines on smooth muscle.

Activation of α receptors by a sympathomimetic drug usually produces a response that includes contraction of smooth muscle in blood vessels (vasoconstriction). Based on differences in their function and location, α receptors have since been subcategorized. Whereas α₁ receptors are excitatory-postsynaptic, α₂ receptors are inhibitory-postsynaptic.
Box 3-1 Categories of Sympathomimetic Amines

<table>
<thead>
<tr>
<th>Direct-Acting</th>
<th>Indirect-Acting</th>
<th>Mixed-Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Tyramine</td>
<td>Metaraminol</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Amphetamine</td>
<td>Ephedrine</td>
</tr>
<tr>
<td>Levonordefrin</td>
<td>Methamphetamine</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Hydroxyamphetamine</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methoxamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3-2 Adrenergic Receptor Activity of Vasoconstrictors

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Levonordefrin</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>


Relative potency of drugs is indicated as follows: ++++, high, ++, intermediate, and +, low.

Activation of $\beta$ receptors produces smooth muscle relaxation (vasodilation and bronchodilation) and cardiac stimulation (increased heart rate and strength of contraction).

Beta receptors are further divided into $\beta_1$ and $\beta_2$: $\beta_1$ are found in the heart and small intestines and are responsible for cardiac stimulation and lipolysis; $\beta_2$, found in the bronchi, vascular beds, and uterus, produce bronchodilation and vasodilation.9

Table 3-2 illustrates the differences in varying degrees of $\alpha$ and $\beta$ receptor activity of three commonly used vasoconstrictors.

Table 3-3 lists the systemic effects, based on $\alpha$ and $\beta$ receptor activity, of epinephrine and norepinephrine.

Release of Catecholamines

Other sympathomimetic drugs, such as tyramine and amphetamine, act indirectly by causing the release of the catecholamine norepinephrine from storage sites in adrenergic nerve terminals. In addition, these drugs may exert direct action on $\alpha$ and $\beta$ receptors.

The clinical actions of this group of drugs therefore are quite similar to the actions of norepinephrine. Successively repeated doses of these drugs will prove to be less effective than those given previously because of depletion of norepinephrine from storage sites. This phenomenon is termed tachyphylaxis and is not seen with drugs that act directly on adrenergic receptors.
Dilutions of Vasoconstrictors

The dilution of vasoconstrictors is commonly referred to as a ratio (e.g., 1 to 1000 [written 1:1000]). Because maximum doses of vasoconstrictors are presented in milligrams, or more commonly today as micrograms (µg), the following interpretations should enable the reader to convert these terms readily:

- A concentration of 1:1000 means that 1 g (1000 mg) of solute (drug) is contained in 1000 mL of solution.
- Therefore, a 1:1000 dilution contains 1000 mg in 1000 mL or 1.0 mg/mL of solution (1000 µg/mL).

Vasoconstrictors, as used in dental local anesthetic solutions, are much less concentrated than the 1:1000 dilution described in the preceding paragraph. To produce these more dilute, clinically safer, yet effective concentrations, the 1:1000 dilution must be diluted further. This process is described here:

- To produce a 1:10,000 concentration, 1 mL of a 1:1000 solution is added to 9 mL of solvent (e.g., sterile water); therefore 1:10,000 = 0.1 mg/mL (100 µg/mL).
- To produce a 1:100,000 concentration, 1 mL of a 1:10,000 concentration is added to 9 mL of solvent; therefore 1:100,000 = 0.01 mg/mL (10 µg/mL).

The milligram per milliliter and µg per milliliter values of the various vasoconstrictor dilutions used in medicine and dentistry are shown in Table 3-4.

The genesis of vasoconstrictor dilutions in local anesthetics began with the discovery of adrenalin in 1897 by Abel. In 1903, Braun suggested using adrenalin as a chemical tourniquet to prolong the duration of local anesthetics.10 Braun recommended the use of a 1:10,000 dilution of epinephrine, ranging to as dilute as 1:100,000, with cocaine in nasal surgery (a highly vascular area). It appears at present that an epinephrine concentration of 1:200,000 provides comparable results, with fewer systemic side effects. The 1:200,000 dilution, which contains 5 µg/mL (or 0.005 mg/mL), has become widely used in both medicine and dentistry and is currently found in articaine, prilocaine, lidocaine (though not in North America), etidocaine, and bupivacaine. In several European and Asian countries, lidocaine with epinephrine concentrations of 1:300,000 and 1:400,000 is available in dental cartridges.

Although it is the most used vasoconstrictor in local anesthetics in both medicine and dentistry, epinephrine is not an ideal drug. The benefits to be gained from adding epinephrine (or any vasoconstrictor, for that matter) to a local anesthetic solution must be weighed against any risks that might be present. Epinephrine is absorbed from the site of injection, just as is the local anesthetic. Measurable epinephrine blood levels are obtained, and these influence the heart and blood vessels. Resting plasma epinephrine levels (39 pg/mL) are doubled after administration of one cartridge of lidocaine with 1:100,000 epinephrine.11 Elevation of epinephrine plasma levels is linearly dose dependent and persists from several minutes to a half-hour.12 Contrary to a previously held position that intraoral administration of usual volumes of epinephrine produced no cardiovascular response, and that patients were more at risk from endogenously released epinephrine than they were from exogenously administered epinephrine,13,14 recent evidence demonstrates that epinephrine plasma levels equivalent to those achieved during moderate to heavy exercise may occur after intraoral
These are associated with moderate increases in cardiac output and stroke volume (see the following section). Blood pressure and heart rate, however, are minimally affected at these dosages.

TABLE 3-3 Systemic Effects of Sympathomimetic Amines

<table>
<thead>
<tr>
<th>Effector Organ or Function</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>+++</td>
<td>0, –</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic arterial</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Diastolic arterial</td>
<td>+, 0, –</td>
<td>++</td>
</tr>
<tr>
<td><strong>Peripheral Circulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>+</td>
<td>0, –</td>
</tr>
<tr>
<td>Cutaneous blood flow</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Splanchnic blood flow</td>
<td>+++</td>
<td>0, +</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchodilation</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td><strong>Genitourinary System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Skeletal Muscle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle blood flow</td>
<td>+++</td>
<td>0, –</td>
</tr>
<tr>
<td><strong>Metabolic Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>++</td>
<td>0, +</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>+++</td>
<td>0, +</td>
</tr>
<tr>
<td>Blood lactic acid</td>
<td>+++</td>
<td>0, +</td>
</tr>
</tbody>
</table>


+, Increase; –, decrease; 0, no effect.
TABLE 3-4 Concentrations of Clinically Used Vasoconstrictors

<table>
<thead>
<tr>
<th>Concentration (Dilution)</th>
<th>Milligrams per Milliliter (mg/mL)</th>
<th>Micrograms per Milliliter (µg/mL)</th>
<th>µg per Cartridge (1.8 mL)</th>
<th>Therapeutic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1000</td>
<td>1.0</td>
<td>1000</td>
<td></td>
<td>Epinephrine—Emergency medicine (IM/SC anaphylaxis)</td>
</tr>
<tr>
<td>1:2500</td>
<td>0.4</td>
<td>400</td>
<td></td>
<td>Phenylephrine</td>
</tr>
<tr>
<td>1:10,000</td>
<td>0.1</td>
<td>100</td>
<td></td>
<td>Epinephrine—Emergency medicine (IV/ET cardiac arrest)</td>
</tr>
<tr>
<td>1:20,000</td>
<td>0.05</td>
<td>50</td>
<td>90</td>
<td>Levonordefrin—Local anesthetic</td>
</tr>
<tr>
<td>1:30,000</td>
<td>0.033</td>
<td>33.3</td>
<td>73 (2.2-mL cartridge)</td>
<td>Norepinephrine—Local anesthetic</td>
</tr>
<tr>
<td>1:50,000</td>
<td>0.02</td>
<td>20</td>
<td>36</td>
<td>Epinephrine—Local anesthetic</td>
</tr>
<tr>
<td>1:80,000</td>
<td>0.0125</td>
<td>12.5</td>
<td>27.5 (2.2-mL cartridge)</td>
<td>Epinephrine—Local anesthetic (United Kingdom)</td>
</tr>
<tr>
<td>1:100,000</td>
<td>0.01</td>
<td>10</td>
<td>18</td>
<td>Epinephrine—Local anesthetic</td>
</tr>
<tr>
<td>1:200,000</td>
<td>0.005</td>
<td>5</td>
<td>9</td>
<td>Epinephrine—Local anesthetic</td>
</tr>
<tr>
<td>1:400,000</td>
<td>0.0025</td>
<td>2.5</td>
<td>4.5</td>
<td>Epinephrine—Local anesthetic</td>
</tr>
</tbody>
</table>

In patients with preexisting cardiovascular or thyroid disease, the side effects of absorbed epinephrine must be weighed against those of elevated local anesthetic blood levels. It is currently thought that the cardiovascular effects of conventional epinephrine doses are of little practical concern, even in patients with heart disease. However, even following usual precautions (e.g., aspiration, slow injection), sufficient epinephrine can be absorbed to cause sympathomimetic reactions such as apprehension, tachycardia, sweating, and pounding in the chest (palpitation)—the so-called epinephrine reaction.

Intravascular administration of vasoconstrictors and their administration to sensitive individuals (hyperresponders), or the occurrence of unanticipated drug–drug interactions, can however produce significant clinical manifestations. Intravenous administration of 0.015 mg of epinephrine with lidocaine results in an increase in the heart rate ranging from 25 to 70 beats per minute, with elevations in systolic blood from 20 to 70 mm Hg. Occasional rhythm disturbances may be observed, and premature ventricular contractions (PVCs) are most often noted.

Other vasoconstrictors used in medicine and dentistry include norepinephrine, phenylephrine, levonordefrin, and felypressin. Norepinephrine, lacking significant $\beta_2$ actions, produces intense peripheral vasoconstriction with possible dramatic elevation of blood pressure, and is associated with a side effect ratio nine times higher than that of epinephrine. Although it is currently available in some countries in local anesthetic solutions, the use of norepinephrine as a vasopressor in dentistry is diminishing and cannot be recommended. The use of a mixture of epinephrine and norepinephrine is to be absolutely avoided. Phenylephrine, a pure $\alpha$-adrenergic agonist, theoretically possesses advantages over other vasoconstrictors. However, in clinical trials, peak blood levels of lidocaine were actually higher with phenylephrine 1:20,000 (lidocaine blood level = 2.4 µg/mL) than with epinephrine 1:200,000 (1.4 µg/mL). The cardiovascular effects of levonordefrin...
most closely resemble those of norepinephrine. Felypressin was shown to be about as effective as epinephrine in reducing cutaneous blood flow.

Epinephrine remains the most effective and the most used vasoconstrictor in medicine and dentistry.

**Pharmacology of Specific Agents**

The pharmacologic properties of the sympathomimetic amines commonly used as vasoconstrictors in local anesthetics are reviewed. Epinephrine is the most useful and represents the best example of a drug mimicking the activity of sympathetic discharge. Its clinical actions are reviewed in depth. The actions of other drugs are compared with those of epinephrine.

**Epinephrine**

**Proprietary Name**

Adrenalin.

**Chemical Structure**

Epinephrine as the acid salt is highly soluble in water. Slightly acid solutions are relatively stable if they are protected from air. Deterioration (through oxidation) is hastened by heat and the presence of heavy metal ions. Sodium bisulfite is commonly added to epinephrine solutions to delay this deterioration. The shelf life of a local anesthetic cartridge containing a vasoconstrictor is somewhat shorter (18 months) than that of a cartridge containing no vasoconstrictor (36 months).

![Chemical structure of epinephrine](image)

**Source**

Epinephrine is available as a synthetic and is also obtained from the adrenal medulla of animals (epinephrine constitutes approximately 80% of adrenal medullary secretions). It exists in both levorotatory and dextrorotatory forms; the levorotatory form is approximately 15 times as potent as the dextrorotatory form.

**Mode of Action**

Epinephrine acts directly on both α- and β-adrenergic receptors; β effects predominate.
Systemic Actions

Myocardium

Epinephrine stimulates $\beta_1$ receptors of the myocardium. There is a positive inotropic (force of contraction) and a positive chronotropic (rate of contraction) effect. Both cardiac output and heart rate are increased.

Pacemaker Cells

Epinephrine stimulates $\beta_1$ receptors and increases the irritability of pacemaker cells, leading to an increased incidence of dysrhythmias. Ventricular tachycardia (VT) and premature ventricular contractions (PVCs) are common.

Coronary Arteries

Epinephrine produces dilation of the coronary arteries, increasing coronary artery blood flow.

Blood Pressure

Systolic blood pressure is increased. Diastolic pressure is decreased when small doses are administered because of the greater sensitivity to epinephrine of $\beta_2$ receptors compared with $\alpha$ receptors in vessels supplying the skeletal muscles. Diastolic pressure is increased with larger epinephrine doses because of constriction of blood vessels supplying the skeletal muscles caused by $\alpha$ receptor stimulation.

Cardiovascular Dynamics

The overall action of epinephrine on the heart and cardiovascular system is direct stimulation:

- Increased systolic and diastolic pressures
- Increased cardiac output
- Increased stroke volume
- Increased heart rate
- Increased strength of contraction
- Increased myocardial oxygen consumption

These actions lead to an overall decrease in cardiac efficiency.

The cardiovascular responses of increased systolic blood pressure and increased heart rate develop with the administration of one to two dental cartridges of a 1:100,000 epinephrine dilution. Administration of four cartridges of 1:100,000 epinephrine will bring about a slight decrease in diastolic blood pressure.
Vascuclature

The primary action of epinephrine is on smaller arterioles and precapillary sphincters. Blood vessels supplying the skin, mucous membranes, and kidneys primarily contain α receptors. Epinephrine produces constriction in these vessels. Vessels supplying the skeletal muscles contain both α and β₂ receptors, with β₂ predominating. Small doses of epinephrine produce dilation of these vessels as a result of β₂ actions. β₂ receptors are more sensitive to epinephrine than are α receptors. Larger doses produce vasoconstriction because α receptors are stimulated.

Hemostasis

Clinically, epinephrine is used frequently as a vasoconstrictor for hemostasis during surgical procedures. Injection of epinephrine directly into surgical sites rapidly produces high tissue concentrations, predominant α receptor stimulation, and hemostasis. As epinephrine tissue levels decrease over time, its primary action on blood vessels reverts to vasodilation because β₂ actions predominate; therefore it is common for some bleeding to be noted at about 6 hours after a surgical procedure. In a clinical trial involving extraction of third molars, postsurgical bleeding occurred in 13 of 16 patients receiving epinephrine with their local anesthetic for hemostasis, whereas 0 of 16 patients receiving local anesthetic without vasoconstrictor (mepivacaine plain) had bleeding 6 hours post surgery. Additional findings of increased postsurgical pain and delayed wound healing were noted in the epinephrine-receiving group.

Respiratory System

Epinephrine is a potent dilator (β₂ effect) of bronchiole smooth muscle. It is an important drug for management of more refractory episodes of bronchospasm (e.g., status asthmaticus).

Central Nervous System

In usual therapeutic dosages, epinephrine is not a potent central nervous system (CNS) stimulant. Its CNS-stimulating actions become prominent when an excessive dose is administered.

Metabolism

Epinephrine increases oxygen consumption in all tissues. Through β action, it stimulates glycogenolysis in the liver and skeletal muscle, elevating blood sugar levels at plasma epinephrine concentrations of 150 to 200 pg/mL. The equivalent of four dental local anesthetic cartridges of 1:100,000 epinephrine must be administered to elicit this response.

Termination of Action and Elimination

The action of epinephrine is terminated primarily by its reuptake by adrenergic nerves. Epinephrine that escapes reuptake is rapidly inactivated in the blood by the enzymes catechol-O-methyltransferase
(COMT) and monoamine oxidase (MAO), both of which are present in the liver. Only small amounts (approximately 1%) of epinephrine are excreted unchanged in the urine.

Side Effects and Overdose

The clinical manifestations of epinephrine overdose relate to CNS stimulation and include increasing fear and anxiety, tension, restlessness, throbbing headache, tremor, weakness, dizziness, pallor, respiratory difficulty, and palpitation.

With increasing levels of epinephrine in the blood, cardiac dysrhythmias (especially ventricular) become more common; ventricular fibrillation is a rare but possible consequence. Dramatic increases in both systolic (>300 mm Hg) and diastolic (>200 mm Hg) pressures may be noted and have led to cerebral hemorrhage. Anginal episodes may be precipitated in patients with coronary artery insufficiency. Because of the rapid inactivation of epinephrine, the stimulatory phase of the overdose (toxic) reaction usually is brief. Vasoconstrictor overdose is discussed in greater depth in Chapter 18.

Clinical Applications

• Management of acute allergic reactions
• Management of refractory bronchospasm (status asthmaticus)
• Management of cardiac arrest
• As a vasoconstrictor, for hemostasis
• As a vasoconstrictor in local anesthetics, to decrease absorption into the cardiovascular system
• As a vasoconstrictor in local anesthetics, to increase depth of anesthesia
• As a vasoconstrictor in local anesthetics, to increase duration of anesthesia
• To produce mydriasis

Availability in Dentistry

Epinephrine is the most potent and widely used vasoconstrictor in dentistry. It is available in the following dilutions and drugs:
**Epinephrine Dilution Local Anesthetic (generic)**

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Anesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:50,000</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>1:80,000</td>
<td>Lidocaine (lignocaine) (United Kingdom)</td>
</tr>
<tr>
<td>1:100,000</td>
<td>Articaine</td>
</tr>
<tr>
<td>1:200,000</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>1:200,000</td>
<td>Articaine</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine</td>
</tr>
<tr>
<td></td>
<td>Etidocaine†</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
</tr>
<tr>
<td></td>
<td>Mepivacaine*</td>
</tr>
<tr>
<td>1:300,000</td>
<td>Prilocaine</td>
</tr>
<tr>
<td>1:400,000</td>
<td>Articaine*</td>
</tr>
</tbody>
</table>

* Not available in the United States (August 2011).
† No longer marketed in the United States (2002).

**Maximum Doses**

The least concentrated solution that produces effective pain control should be used. Lidocaine is available with two dilutions of epinephrine—1:50,000 and 1:100,000—in the United States and Canada, and with 1:80,000, 1:200,000, and 1:300,000 dilutions in other countries. The duration of effective pulpal and soft tissue anesthesia is equivalent with all forms. Therefore it is recommended (in North America) that the 1:100,000 epinephrine concentration be used with lidocaine when extended pain control is necessary. Where 1:200,000 or 1:300,000 epinephrine is available with lidocaine, these concentrations are preferred for pain control.30

The dosages in Table 3-5 represent recommended maximums as suggested by this author and others.31 They are conservative figures but still provide the dental practitioner with adequate volumes to produce clinically acceptable anesthesia. The American Heart Association as far back as 1964 stated that “the typical concentrations of vasoconstrictors contained in local anesthetics are not contraindicated in patients with cardiovascular disease so long as preliminary aspiration is practiced, the agent is injected slowly, and the smallest effective dose is administered.”32 In 1954 the New York Heart Association recommended that maximal epinephrine doses be limited to 0.2 mg per appointment.33 In the following years, the American Heart Association recommended the restriction of epinephrine in local anesthetics when administered to patients with ischemic heart disease.34

More recently, the Agency for Healthcare Research and Quality (AHRQ) reviewed the published literature on the subject of the effects of epinephrine in dental patients with high blood pressure.35 The report reviewed six studies that evaluated the effects of dental treatment (extraction of teeth) in hypertensive patients when they received local anesthetics with and without epinephrine. Results suggest that hypertensive subjects undergoing an extraction experience small increases in systolic blood pressure and heart rate associated with the use of a local anesthetic containing epinephrine. These increases associated with the use of epinephrine occur in addition to increases in systolic and diastolic blood pressures and heart rate associated with undergoing the procedure without