Anesth Prog 38:128–141 1991

Local Anesthetics

John A. Yagiela, DDS, PhD
School of Dentistry and School of Medicine, University of California, Los Angeles, Los Angeles, California

Local anesthetics applied in appropriate concentrations reversibly depress conduction in peripheral nervous tissue. Because of their enviable record of efficacy and safety in producing insensibility to pain in discrete regions of the body, local anesthetics are administered in more ways than perhaps any other group of therapeutic agents. As all excitable tissues are susceptible to local anesthetic block, these drugs also find use systemically as antiarrhythmic agents and as adjuncts for general anesthesia.

Cocaine, the original local anesthetic, was first injected for mandibular anesthesia by William Halsted several months after Carl Koller's demonstration of its anesthetic property was made public in September 15, 1884.[1] Pioneers including Halsted, James Corning, and August Bier soon developed many of the basic techniques for administration still used today.[2] The liabilities of cocaine anesthesia were also soon recognized, leading men like Heinrich Braun to employ formulations containing epinephrine to retard absorption of the local anesthetic from the injection site and Alfred Einhorn to develop procaine and other nonaddicting alternatives to cocaine.[3] Table 1 catalogs important landmarks in the development of local anesthesia.

MECHANISM OF LOCAL ANESTHESIA

All local anesthetics in clinical practice inhibit nerve conduction by interfering with the entry of sodium ions (Na^+) through the nerve cell membrane. While a number of different theories have been proposed to account for this action, the preponderance of evidence suggests that local anesthetics act directly on Na^+ channels.[4–5]

As illustrated in Figure 1, the Na^+ channel typically cycles through three primary configurations during an action potential. In the quiescent nerve, most Na^+ channels are in a resting, closed state. Partial depolarization of the membrane caused by electrotonic currents traveling in front of an advancing action potential induces these channels to open, leading to an explosive depolarization and propagation of the action potential. Almost immediately, however, these same channels become inactivated, preventing continued Na^+ influx regardless of any further stimulation. Reconversion from the refractory inactivated state to the responsive resting state occurs only after the transmembrane potential has returned to normal.

Local anesthetics bind to the Na^+ channel, possibly within the channel pore itself, and disrupt the normal cycling process. If sufficient channels are blocked over a sufficient length of nerve, the action potential is prevented from proceeding down the neuron. Figure 2 illustrates a developing anesthetic block in a single neuron.

It is not yet established how local anesthetic binding to the channel prevents Na^+ entry. Physical occlusion of the channel pore may occur, but analysis of gating currents suggests that the predominant mechanism is prevention of the conformational transitions depicted in Figure 1. Gating currents are generated by the outward displacement of positively charged amino acid residues of the Na^+ channel during the activation process and their inward displacement upon return to the resting state. Local anesthetics diminish gating currents in concert with their potential to inhibit the action potential.[6–7] The resultant inability of the channel to open precludes regeneration of the action potential whether or not the local anesthetic physically blocks the pore.

Because clinically useful local anesthetics are fairly heterogeneous in structure, it is safe to conclude that the channel binding site lacks the stereospecificity normally ascribed to a drug receptor. (The term "local anesthetic receptor" is, in fact, rarely used.) Nevertheless, the location of the binding site within the membrane, and perhaps within the pore itself, places some structural limitations on drugs intended for use as local anesthetics. As illustrated by lidocaine (Figure 3), the typical local anesthetic is amphipathic, with a lipophilic aromatic ring structure at one end of the molecule and a hydrophilic amino group at the other end, which confers water solubility to the drug when charged by the reversible binding of a hydrogen ion. An intermediate linkage consisting of an amide, ester, or ether moiety bonded to a short alkyl chain provides the appropriate separation between the lipophilic and hydrophilic ends. Consistent with the need to have both sufficient water solubility to avoid precipita-

Address correspondence to Dr. John A. Yagiela, UCLA School of Dentistry, Center for the Health Sciences, Los Angeles, CA 90024.

ISSN 0003-3006/91/$3.50

Table 1. Pioneers and Landmarks in the Development of Local Anesthesia

Year	*Person*	*Contribution*
1859	Niemann	Isolation of cocaine in pure form; recognition of its topical anesthetic property
1884	Koller	Clinical introduction of cocaine topical anesthesia
1884	Halsted	Clinical introduction of cocaine regional anesthesia
1885	Corning	Application of a tourniquet to retard cocaine absorption; first use of spinal anesthesia
1898	Bier	Spinal anesthesia via lumbar puncture
1901	Braun	Use of epinephrine as a "chemical tourniquet"
1904	Einhorn	Synthesis of procaine
1908	Bier	Intravenous regional anesthesia with procaine
1920	Cook Lab.	Marketing of the anesthetic cartridge and syringe
1943	Lofgren	Synthesis of lidocaine
1947	Novocol Co.	Marketing of the dental aspirating syringe
1957	Ekenstam	Synthesis of bupivacaine
1959	Cook-Waite, Roehr Co.	Marketing of the disposable sterile needle

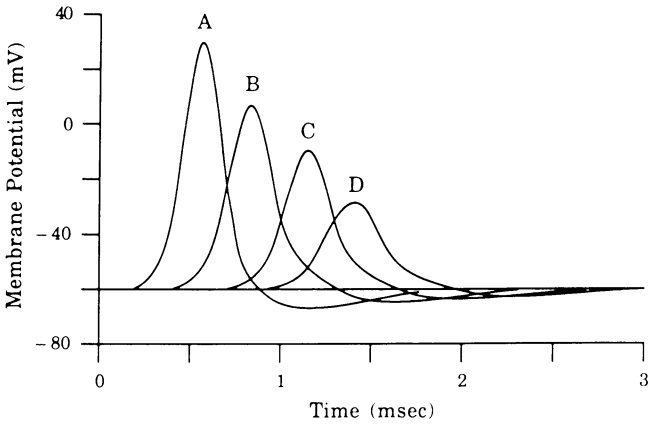
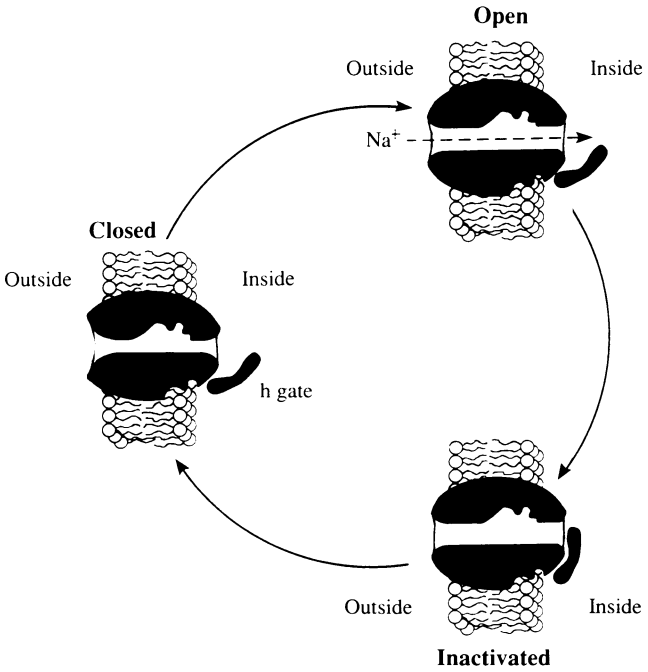


Figure 2. Developing local anesthetic block in a single neuron. A. Normal action potential. B. Incipient local anesthetic block. The height of the action potential falls as sodium channels are prevented from opening. The rate of conduction is likewise inhibited. C. Progressive decline in the action potential in response to the developing local anesthetic block. D. Cessation of axonal conduction. Enough channels are blocked that electrotonic depolarization of the adjacent, unaffected membrane will be insufficient to generate a self-replicating action potential.

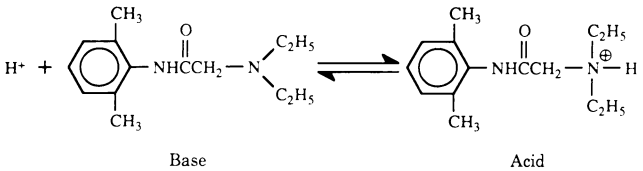
Figure 1. Conformational changes of the sodium channel during an action potential.



tion upon injection into interstitial fluid, and satisfactory lipid solubility to penetrate the hydrophobic nerve sheath and axolemma, local anesthetics have a dissociation constant (pK_a) in the 7.5 to 9.0 range, which permits the neutral and charged forms to coexist at tissue pH. Size constraints cluster the molecular weights of these drugs to between 200 and 300 daltons.

Figure 4 illustrates two drugs that differ in structure from the typical local anesthetic. Benzocaine is a topical local anesthetic lacking the amino terminus of its parent drug, procaine; QX-314, a drug used solely for research purposes, is the permanently charged, quaternary amine derivative of lidocaine. Largely insoluble in aqueous media, benzocaine is unsuitable for parenteral injection. Unable to penetrate the nerve sheath, QX-314 is only active

Figure 3. Structural formulas of lidocaine in the uncharged, base form and in the charged, acidic form. Assuming a tissue pH of 7.4 and a dissociation constant (pK_a) of 7.8, the acid/base ratio is 2.5/1 (72% of the drug is charged and 28% uncharged), as calculated by the Henderson-Hasselbalch equation ($pH = pK_a + \log[base/acid]$).



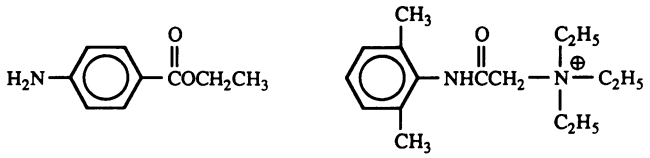


Figure 4. Structural formulas of the nonamphipathic local anesthetics benzocaine and QX-314.

when injected into the axoplasm. An important corollary of these findings is that both the free base and charged acidic forms of the conventional local anesthetic can block Na^+ channels.

FACTORS INFLUENCING LOCAL ANESTHETIC BLOCKADE

Although local anesthetics act similarly to inhibit nerve conduction in vitro, a number of variables exist that strongly influence the degree and even the type of blockade observed clinically. Variables such as concentration and dose are easily controlled; others, like potency, are inherent features of the anesthetic selected; and still others, for example, tissue pH and barriers to anesthetic spread, are intrinsic to the patient. Several determinants of local anesthetic activity have been extensively studied in recent years and deserve special comment.

Anesthetic Potency and "Minimum Inhibitory Concentration"

Local anesthetics vary in their innate ability to block nerve conduction. Experimental studies and clinical observations agree that anesthetic potencies differ more than tenfold.[8] As revealed in Table 2, anesthetic potency is most closely associated with the lipid: buffer distribution coefficient (Q), which estimates the relative tendency for an anesthetic to associate with the nerve membrane at a given temperature and pH.[9] In a manner analogous to the minimum alveolar concentration (MAC) for general anesthetics, attempts have been made to define local anesthetic potency in terms of the "minimum blocking concentration" (C_m), the lowest concentration necessary for blocking a given nerve in vitro within a selected timeframe.[10] Unfortunately, this approach has proved unsatisfactory. As is discussed below, the concentration required for anesthesia is highly dependent on the length of nerve exposed to the anesthetic, the amount of impulse traffic flowing through the nerve, and the physiologic state of the nerve. Variables in drug distribution and differences in anesthetic susceptibility independent of fiber type further weaken the concept of C_m as a useful predictor of local anesthetic effect.

Differential Nerve Block and Critical Length

The notion that anesthetic susceptibility varies with fiber size arose over a half century ago from the discovery that the rate of onset of cocaine anesthesia in peripheral nerve was diameter dependent.[11] It gained strong support from observations of patients receiving spinal and epidural anesthesia who lost autonomic control and the sensations of nociception and temperature (small fiber functions) but maintained motor control and the sensations of touch and pressure (large fiber functions). With strong face validity, it is perhaps understandable that contemporary literature is still replete with pronouncements of the positive correlation between C_m and fiber diameter even though carefully designed experiments involving individual axons have consistently shown that no such relationship exists.[12–13]

In a seminal paper, Franz and Perry[12] found that an absolute differential nerve block could be obtained, but

Table 2. Physicochemical and Clinical Properties of Local Anesthetics

Drug	*pK_a**	*Rate of onset*	*Q**	*Relative potency†*	*Duration of anesthesia*	*MW*	*Phasic block§*
Amides							
Lidocaine	7.8	fast	110	2	moderate	234	low
Bupivacaine	8.1	med	560	8	long	288	high
Esters							
Procaine	8.9	med	3	1	short	236	med
Tetracaine	8.4	med	541	8	long	264	med

*Data from Butterworth and Strichartz.[5] pK_a (dissociation constant) and Q (octanol: buffer distribution coefficient) measured at 36° C in buffered (pH 7.4) isotonic saline solution.

†Data from Covino.[8] Tonic block; peripheral nerve in vitro.

§Data from Courtney.[9] Potency determined in papillary muscle in vitro.

only when the length of axon exposed to the local anesthetic was restricted (eg, to 2 mm). Given that a minimum of three nodes had to be fully blocked before conduction would fail, and that the internodal distance varies with fiber diameter, they concluded that there is a size-dependent "critical length" of anesthetic exposure necessary to block a given nerve. Small fibers would be blocked before large fibers because small areas of effective concentrations of anesthetic would be achieved in peripheral nerves before large areas, and small fibers would be affected longer because small areas of effective concentrations would persist longer into the recovery phase. An absolute differential block, however, would be expected only when anatomical barriers to diffusion limited anesthetic exposure, as in the case of epidural anesthesia.[13] With the recent demonstration[14] that C_m varies inversely with the length of axon exposed up to 3 cm, the critical length hypothesis has been modified by Fink[13] to apply to situations, such as subarachnoid anesthesia, in which decremental conduction occurring over more than three nodes may still result in differential blockade because smaller fibers would have more nodes affected, leading to a progressive decline in the action potential to below threshold.

Intensity and Frequency of Stimulation

In the early stages of anesthetic block it is sometimes observed that patients lose sensitivity to small painful stimuli, such a pin pricks, but remain responsive to more intense stimuli, such as surgical incision. A number of explanations may account for this finding, including the fact that the stronger stimulus undoubtedly activates more fibers, some of which are not yet blocked by the anesthetic. In the case of topical or infiltration anesthesia, in which the anesthetic is locally active, a more intense stimulus may lead to greater initial depolarization of the free nerve endings, overcoming the inhibitory effect of the local anesthetic. Some authors[10,15] have argued that the more intense stimulus causes a train of impulses to be generated, some of which are conducted when a single impulse is not. The assumption is that a temporal summation of subthreshold responses allows every third or fourth action potential to surmount the block. This explanation, however, runs contrary to the now well-established phenomenon of frequency-dependent block.

Frequency-dependent block, otherwise referred to as use-dependent block or phasic block, denotes an increase in anesthetic effect as a nerve is repeatedly stimulated. Depending on the local anesthetic agent and the rate of nerve stimulation, frequency-dependent block can vary enormously, from contributing little to the anesthetic effect to providing virtually all of it. Frequency-dependent block is presumably contingent on the relative ability of the anesthetic agent to reach and leave its site of action within the Na^+ channel, as influenced by the various conformational states of the channel (Figure 1).[4] Drugs like QX-314, which are permanently charged, can only reach the site of action when the channel is open (or at least partially activated[5]) and are highly dependent on the frequency of stimulation for blocking the nerve. Benzocaine, without a positive charge, is largely devoid of frequency-dependent blocking activity. For typical anesthetics, which can exist in both charged and uncharged forms, pK_a and, in particular, molecular weight are positively correlated with the tendency to cause frequency-dependent block.[9] Bupivacaine, high in both attributes (Table 2), is well known for eliciting this effect.

The importance of frequency-dependent block is easily illustrated. For example, because nervous transmissions encoded in repeated bursts of depolarization are more susceptible to anesthetic action than are transmissions that occur at low frequency, local anesthetics may block noxious stimuli and sympathetic nervous system outputs preferentially over somatomotor activity simply because of differences in transmission frequency.[16] Additionally, the antiarrhythmic action of lidocaine may be ascribed to a selective development of Na^+ channel inhibition during ventricular tachycardia, and the cardiotoxic effect of bupivacaine may be correlated with its tendency to cause frequency-dependent block at even resting heart rates.[17]

Inflammation and Tissue pH

Clinical observations and experimental reports agree that the presence of inflammation can greatly impair local anesthetic efficacy. Inflammation is associated with a number of physiologic and pathologic disturbances. Certainly, the most publicized of these with respect to local anesthetic action is tissue acidity. A low pH in the extracellular space impairs the ability of local anesthetics to cross the nerve sheath and membrane because it reduces the proportion of anesthetic in the lipophilic, free base form. A fall in pH from 7.4 to 6.4, for instance, reduces the proportion of the base form of lidocaine in the extracellular fluid from 28% to 4%, a sevenfold reduction. Not only will this effect retard the onset of anesthesia, it may preclude anesthesia altogether. Should the intraneuronal pH be unaffected by the inflammation, the concentration of local anesthetic will be depressed even after full equilibration by "ion trapping" within the interstitial space. An enhanced uptake of local anesthetic because of increased local blood flow in the inflamed tissue may also contribute to an inability to achieve anesthetic concentrations within axons.

Hyperalgesia is commonly associated with inflammatory states. Prostaglandins, kinins, and other substances produced during inflammation activate nociceptors di-

rectly and/or make them more responsive to additional stimuli. In clinical situations where local anesthetic blockade is incomplete, the enhanced recruitment of fibers for a given operative stimulus may lead to the perception of pain. Several studies have suggested that certain chemicals produced during inflammation may directly interfere with conduction blockade.[18] These substances may include peptides, prostaglandins, and derivatives of adenosine. The finding that Na^+ channels are subject to phosphorylation raises the possibility of direct hormonal regulation of neuronal depolarization.[19]

UPTAKE, DISTRIBUTION, AND ELIMINATION

The processes of absorption, distribution, metabolism, and excretion are important to consider because they dictate whether or not systemic effects will follow local anesthetic administration. The rate of absorption from the injected tissue also plays a role in the duration of anesthesia.

A number of variables influence the uptake of local anesthetics. These include the affinity of the anesthetic for the local tissues, the tissue blood flow, the effect of the anesthetic agent on the local circulation, and the coadministration of a vasoconstrictor. In general, drugs injected for dental anesthesia are absorbed fairly rapidly, with peak plasma concentrations occurring within 15 to 30 min.

As a local anesthetic is absorbed into the systemic circulation, a portion of it is reversibly bound to plasma proteins, principally α_1-acid glycoprotein and, to a lesser extent, albumin. The local anesthetic also is taken up by red blood cells. Plasma protein binding appears to be related to the lipid : buffer distribution coefficient. About 95% of the highly lipophilic etidocaine and bupivacaine is bound at nontoxic concentrations; comparable figures for the moderately lipophilic lidocaine and the modestly lipophilic prilocaine are 70% and 55%, respectively.[20] The blood : plasma ratio follows a reverse relationship, with prilocaine exhibiting a value of 1.0, lidocaine 0.84, and the two lipophilic drugs below 0.75.

As the anesthetic is absorbed, it is distributed to virtually all tissues of the body. Normally, the rate of distribution is sufficiently fast with respect to absorption that transient toxic concentrations do not occur in any specific tissue. If the drug is injected intravascularly, however, a pattern of sequential distribution emerges in which the anesthetic is first taken up by the lungs, rapidly distributed to other organs with relatively large blood supplies (rapidly equilibrating tissues: brain, heart, liver, kidneys, spleen), and then redistributed to muscle and fat (Figure 5).[21] Although the lungs serve a potentially useful role in buffering an injected bolus of anesthetic within the first

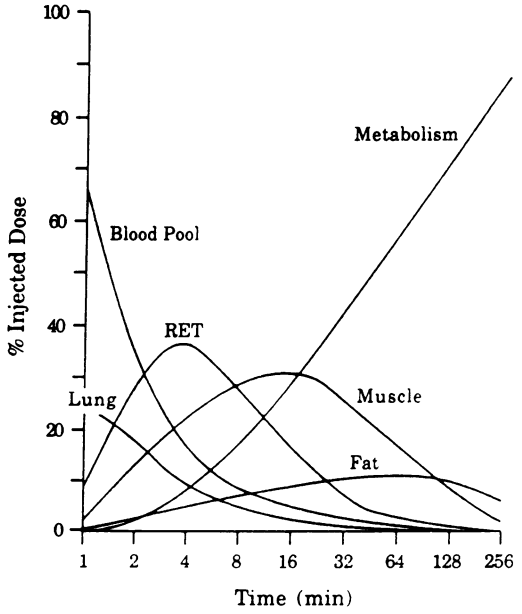


Figure 5. Distribution and metabolism of lidocaine after an intravenous infusion lasting 1 min. RET = rapidly equilibrating tissues (including the brain, heart, liver, and kidneys). Metabolism indicates the percentage of the injected dose that has been metabolized. Reproduced, with permission, from Benowitz et al.[21]

minute,[22] the rapid uptake of drug into the brain and heart can lead to exaggerated, though short lived, systemic effects.

The metabolic fate of local anesthetics depends on their chemical classification. Procaine, benzocaine, tetracaine, and related ester derivatives of *p*-aminobenzoic acid are predominantly hydrolyzed by plasma pseudocholinesterase. Hepatic esterase activity is more important with certain other ester-type anesthetics. In all instances, however, hydrolysis results in the loss of local anesthetic activity.

The normally rapid hydrolysis of procaine-like drugs in plasma (elimination half-time of procaine can be as low as 43 sec) has inhibited pharmacokinetic studies of ester local anesthetics. Drugs known to retard ester metabolism include the anticholinesterase agents (eg, neostigmine, echothiophate), several insecticides (eg, parathion), and, surprisingly, amide local anesthetics (especially bupivacaine).[20] Of course, the greatest deficit in ester metabolism occurs in those individuals with atypical pseudocholinesterase activity.

Amide anesthetics undergo a complex pattern of biotransformation. Other than prilocaine, which is metabolized in part by the lung and/or kidney, amides are broken down exclusively in the liver. The initial reaction usually involves microsomal N-dealkylation, converting the tertiary amine of drugs like lidocaine and bupivacaine

Table 3. Pharmacokinetic Parameters of Amide Local Anesthetics in Humans*

Drug	$t_{1/2}$ (min)	VDss (L)	Cl (L/min)
Lidocaine	96	91	0.95
Mepivacaine	114	84	0.78
Prilocaine	93	261	2.84
Bupivacaine	162	73	0.58
Etidocaine	162	133	1.11

*$t_{1/2}$ = elimination half-time; VD_{ss} = volume of distribution at steady state; Cl = clearance. Data from Tucker and Mather[23–24] and from Arthur et al.[25]

to secondary amines. Often, these initial metabolites retain significant activity and contribute to systemic reactions. A second N-dealkylation may occur, or the molecule may be hydrolyzed (and inactivated) by hepatic amidase activity. Prilocaine, a secondary amine to begin with, largely undergoes hydrolysis without prior N-dealkylation. Hydroxylation of the aromatic ring may take place any time during this sequence, and a high proportion of the derivatives is conjugated with glucuronic acid. Very little local anesthetic is excreted unchanged.

The pharmacokinetic profile of amide local anesthetics (Table 3) bears no obvious relationship to any single physicochemical property (Table 2).[23–25] Whereas etidocaine and bupivacaine share similar half-times of elimination, etidocaine enjoys a significantly greater hepatic clearance than does bupivacaine, but is also sequestered much more by peripheral tissues. The unusually large clearance of prilocaine reflects the extrahepatic elimination of the drug. Because the hepatic clearances of lidocaine and etidocaine approach 75% of the total liver blood flow, anything that alters liver blood flow may affect local anesthetic metabolism. On the positive side, a high-protein meal can increase lidocaine metabolism 20% on average by stimulating portal circulation.[26] More important, however, are situations in which metabolism is impaired. Disorders known to decrease liver blood flow include cirrhosis, congestive heart failure, and hypotension. Hypotensive patients in the sitting position may be especially prone to local anesthetic toxicity, because an acute fall in the apparent volume of distribution has been linked to an 80% increase in the peak lidocaine concentration after intravenous injection.[27] Drugs that have the potential to lower hepatic blood flow include the β-adrenergic blocking drug propranolol. However, a direct effect on local anesthetic metabolism probably accounts for most of the 50% reduction in lidocaine clearance caused by propranolol[28] and most if not all of the similar reduction caused by cimetidine, an H_2-antihistamine.[29] Old age has also been shown to retard lidocaine metabolism, although controversy remains as to whether the deficit is caused by an impairment in hepatic clearance[30] or an increase in the apparent volume of distribution.[31]

SYSTEMIC EFFECTS

Once absorbed into the systemic circulation, a local anesthetic may interact with Na^+ channels in all excitable tissues. Neurons in the central nervous system (CNS) are probably the most responsive, but prominent actions also include the heart and vasculature. Not all systemic reactions involve Na^+ conductance changes, however, which raises the possibility for nonexcitable tissues to interact with local anesthetics.

Central Nervous System

Dose-dependent effects of local anesthetics on the CNS are listed in Table 4, using lidocaine as a representative drug. Blood concentrations routinely associated with clinical doses in dentistry cause only minimal alterations in mental activity. Even the intravenous injection of 1 mg/kg lidocaine to control ventricular tachyarrhythmias, which results in a peak blood concentration of about 4.5 μg/ml,[32] normally elicits only potentially beneficial effects in the CNS: analgesia, anticonvulsant activity, and perhaps mild sedation. Increasingly excessive dosages and blood concentrations, however, start to depress vital areas of the brain. Thus, confusion, somnolence, and respiratory depression may develop. Excitatory phenomena—dysphoria, auditory and visual disturbances, and signs of motor hyperactivity—also occur, arising from the selective depression of inhibitory centers within the cerebral cortex. These excitatory responses tend to predominate and evolve into generalized seizures when the amygdaloid complex is sufficiently released from tonic inhibition to begin depolarizing spontaneously. Postictally, complete respiratory arrest may ensue in response to cerebral hypoxia, hypercarbia, and the continued uptake of local anesthetic into the brain.

Table 4. Effects of Lidocaine on the Central Nervous System and Cardiovascular System

Concentration (μg/ml)	*CNS effect**	*CVS effect**
< 5	Anticonvulsant activity Mild sedation Analgesia	Antiarrhythmic activity Mild increases in mean BP with similar increases in cardiac output or peripheral vascular resistance
5–10	Lightheadedness, slurred speech, drowsiness, euphoria Nausea, dysphoria, sensory disturbances, diplopia, muscle twitching	Cardiovascular instability
10–15	Disorientation Uncontrollable tremors Respiratory depression Tonic-clonic seizures	
15–20	Coma Respiratory arrest	
> 20		Profound myocardial depression, vasodilatation Cardiovascular collapse

*CNS and CVS effects are listed in approximate order of occurrence with increasing blood concentration.

Cardiovascular System

Cardiovascular reactions to local anesthetics stem from direct actions on the heart and vascular smooth muscle, from direct actions on sympathetic neurons, and from changes in autonomic function mediated via the CNS. Obviously, the coadministration of a vasoconstrictor such as epinephrine has an additional influence on the ultimate response seen clinically.

Local Anesthetic Effects. As in the CNS, blood concentrations typically observed following regional anesthesia produce only benign alterations in cardiovascular function (Table 4). A centrally mediated increase in sympathetic nervous activity is presumed to be responsible for the mild increase in heart rate, cardiac output, and mean arterial blood pressure reported in some studies.[33] Alternatively, a modest increase in peripheral vascular resistance brought on by a direct stimulation of vascular smooth muscle may predominate, leading to a small decrease in cardiac output.[32] The antiarrhythmic efficacy of lidocaine depends on several cardiac actions.[34] Ectopic pacemaker activity is reduced or eliminated because the drug inhibits spontaneous depolarization during phase 4 of the cardiac action potential. Ventricular tachyarrhythmias are aborted because lidocaine reduces membrane responsiveness to depolarizing stimuli in a frequency-dependent manner. An increase in the effective refractory period/action potential duration ratio also helps to regularize ventricular conduction.

Adverse cardiovascular responses to local anesthetics are generally not manifested unless the blood concentration reaches the convulsant range (10–15 μg/ml for lidocaine). Both hypertensive and hypotensive reactions occur, representing different interplays of the direct depressant actions of the drug on the myocardium, centrally mediated disturbances in autonomic function, and the effects of hypoxia and hypercarbia. With lidocaine and most other local anesthetics, the dose required to induce cardiac arrest experimentally is several times that which produces respiratory arrest. Therefore, profound myocardial depression, vascular dilatation, and cardiovascular collapse are unlikely to occur clinically if the patient's ventilation is adequately supported. This generalization, however, may not hold true for long-acting anesthetics like bupivacaine and etidocaine. Some animal investigations and clinical case reports indicate that these drugs may cause fatal cardiac arrhythmias at dosages more in line with those that trigger seizures and respiratory arrest, especially if hypercarbia, acidosis, and hypoxia are also present.[35–36] As previously mentioned, the penchant for these drugs to induce frequency- dependent block may underlie this enhanced cardiotoxicity. The exact mechanism, however, remains to be determined, with investigators finding evidence to support several disparate theories, from inhibition of myocardial energy production[37] to proposals of a CNS origin for cardiac arrhythmias.[38–39]

Vasoconstrictor Effects. Studies over the last decade have overturned a widely held tenet[40] in clinical dentistry that the amount of epinephrine injected during local

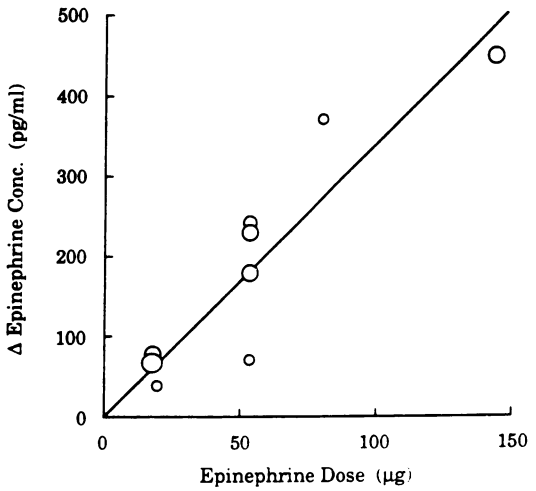


Figure 6. Changes in venous plasma epinephrine after intraoral injection of 2% lidocaine with 1 : 100,000 epinephrine (1 : 25,000 for the 80–μg dose). Each circle indicates the mean value of a group of subjects; the relative size of the circle is proportional to the number of subjects in the group (n = 6 to 14). Data from various sources.[41–46]

anesthesia is low compared to the endogenous release of the hormone and therefore has little or no effect systemically. Figure 6 collates findings from six studies on the effect of intraoral injection of lidocaine with epinephrine on the resting venous plasma concentration of epinephrine.[41–46] With an overall mean epinephrine baseline of 39 pg/ml, regression analysis reveals a linear increase with injected epinephrine such that a single dental cartridge of 2% lidocaine with 1 : 100,000 epinephrine doubles the baseline titer. Venous plasma concentrations associated with the injection of 100 to 150 μg of epinephrine, as often occurs in oral and periodontal surgery, produce concentrations equivalent to that present during heavy exercise.[47]

The absorption of even the small amounts of epinephrine contained in one or two dental cartridges evokes modest but reproducible increases in stroke volume and cardiac output and comparable decreases in peripheral vascular resistance.[48–50] Blood pressure and heart rate are most often minimally affected by these low doses. However, with toxic doses, as may occur when a large volume of anesthetic is accidentally injected into the blood stream, dramatic increases in blood pressure and changes in heart rate (tachycardia, reactive bradycardia, arrhythmias) can develop. Such changes are more likely to occur in patients with pre-existing cardiovascular disease and in individuals taking medications likely to augment adrenergic action (eg, tricyclic antidepressants, nonspecific β-adrenergic blockers).[51]

Comparative information is not readily available on the two vasoconstrictor alternatives to epinephrine: levonordefrin and norepinephrine. It is reasonable to assume that both agents are absorbed in sufficient concentrations after intraoral injections to elicit systemic reactions. Because norepinephrine does not stimulate vasodilative β_2-adrenergic receptors, it tends to increase peripheral vascular resistance and mean blood pressure and reflexively reduce cardiac output and heart rate in dental patients.[50] Levonordefrin, intermediate in its stimulation of β_2 receptors, may mimic either drug, depending on the dose and patient sensitivity. At toxic doses, all three agents exhibit similar pharmacologic profiles.

Miscellaneous Effects

An interesting array of miscellaneous actions has been ascribed to local anesthetics.[8] For instance, local anesthetics have been shown to augment neuromuscular blockade in combination with either depolarizing or nondepolarizing agents. Both pre- and postjunctional effects probably contribute to this action; in the case of succinylcholine, the aforementioned ability of local anesthetics to inhibit pseudocholinesterase may add another dimension to the potentiation.

The ability of amide local anesthetics to perturb calcium metabolism allows these drugs to cause vascular smooth muscle contraction in clinical concentrations and once raised the possibility that malignant hyperthermia might be triggered in susceptible patients. Numerous lines of evidence now indicate this concern is unjustified.[52] Local anesthetics are myotoxic, however, if injected into or adjacent to skeletal muscle.[53] A dose-dependent action on bronchial smooth muscle is similar to that observed in vascular smooth muscle, with low concentrations causing constriction and high concentrations dilation. Attempts to treat bronchial asthma by inhalation of lidocaine mist has proved beneficial in some instances and detrimental in others.[8]

Methemoglobinemia is a special problem with prilocaine but may be also caused by benzocaine and possibly lidocaine.[54–55] Metabolites of these drugs (o-toluidine in the case of prilocaine) upset the balance between oxidation of the iron in hemoglobin to the ferric (Fe^{+++}) state and its enzymatic reduction back to the ferrous (Fe^{++}) form. Cyanosis occurs when the methemoglobin concentration exceeds 1.5 g/dL. Although no association between congenital forms of methemoglobinemia and local anesthetic-induced cyanosis has been drawn, prudence dictates that prilocaine be avoided in such individuals and that benzocaine be used sparingly. Potentially positive interactions between local anesthetics and blood include an antithrombotic effect after surgery[56] and reduction of albumin extravasation in burn injuries.[57]

No discussion of the physiologic consequences of local anesthesia would be complete without some mention of the most common cause of systemic disturbances: psychogenic reactions. Intraoral injection is widely perceived by patients as the single most stressful procedure encountered in routine dentistry. Common responses to this stress include pallor, sweating, nausea, headache, palpitations, hyperventilation, and syncope. Although these reactions as a group are easily managed, life-threatening responses, including cardiac arrest, may occur.[58] The more pronounced a reaction is, the more likely it will be misdiagnosed as drug allergy.

True allergic reactions to local anesthetics are now quite rare in dentistry. The almost complete abandonment of ester anesthetics for regional anesthesia and the removal of paraben preservatives from local anesthetic cartridges are responsible for this improvement in patient safety. The possibility remains, however, for patients to exhibit hypersensitivity to sulfites contained in some anesthetic solutions. Sodium metabisulfite and acetone sodium bisulfite prevent the oxidation of adrenergic vasoconstrictors. While isolated case reports may describe true allergic reactions,[59] most patients affected by sulfites are asthmatics with airways hyperreactive to sulfur dioxide, a breakdown product of inhaled or ingested sulfites.[60] In the most sensitive of these individuals, the response threshold for bronchial constriction is in the 0.5 to 1 mg range, roughly comparable to what is present in a single dental cartridge. Initial use of sulfite-containing anesthetics in the threshold range to gauge patient sensitivity coupled with stepped increases in future appointments is a useful strategy for hyperreactors; total restriction is necessary in the rare but truly allergic patient.

THERAPEUTIC SUGGESTIONS FOR DRUG SELECTION

The selection of drugs for local anesthesia is ideally based on considerations of safety, efficacy, and duration of effect. With the exception of Ravocaine (propoxycaine and procaine), which is best reserved for patients presumed to be allergic to all other alternatives, amides are the only local anesthetics currently marketed for use in single-dose cartridges. Although the amides differ somewhat in relative toxicity, safety issues assume prominence only with respect to special patients: allergic individuals, young children, patients on certain drugs, and patients with significant cardiovascular disease. None of these formulations differs significantly from the rest in nerve block efficacy, and variances in the rate of onset are more dependent on the technique of administration than on the drug injected (with the possible exception of bupivacaine, whose onset may be delayed by 1 to 2 min). Thus, drug selection for intraoral anesthesia often devolves into a decision based on the duration of effect.

Duration Considerations

Table 5 summarizes the durations of pulpal and soft tissue anesthesia after maxillary supraperiosteal injection ("infiltration") and inferior alveolar nerve block. Soft tissue data reflect the authors' synthesis[61] of numerous sources of information; pulpal data represents for the most part a similar compilation by a leading manufacturer of dental anesthetics.[62]

Three crucial factors govern the duration of anesthesia. The first of these is the presence of a vasoconstrictor.

Table 5. Average Durations of Local Anesthesia

	Maxillary infiltration		*Inferior alveolar block*	
Preparation	*Pulpal tissue*	*Soft tissue*	*Pulpal tissue*	*Soft tissue*
2% lidocaine HCl; 1:100,000–1:50,000 epinephrine	60	170	85	190
2% mepivacaine HCl; 1:20,000 levonordefrin	50	130	75	185
3% mepivacaine	25	90	40	165
4% prilocaine	20	105	55	190
4% prilocaine; 1:200,000 epinephrine	40	140	60	220
0.5% bupivacaine; 1:200,000 epinephrine	40	340	240	440
1.5% etidocaine; 1:200,000 epinephrine	30	280	240	470
0.4% propoxycaine, 2% procaine; 1:20,000 levonordefrin or 1:30,000 norepinephrine	40	145	60	175

Epinephrine, levonordefrin, and norepinephrine, all powerful α-adrenergic receptor agonists, strongly reduce blood flow in the area of injection. This action helps to retain the local anesthetic locally, giving it time to accumulate in neuronal tissues, from which it slowly diffuses. Prolongation of anesthesia occurs uniformly with maxillary supraperiosteal injections, but the failure of epinephrine to alter prilocaine anesthesia in the mandible underscores the second governing factor, the site of injection.

Site-specific influences on local anesthesia are often overlooked, as in the use of formulations without vasoconstrictor to "shorten" the duration of mandibular anesthesia and drugs like bupivacaine for "long-duration" maxillary supraperiosteal anesthesia. In the case of intraligamentary anesthesia, controversy still exists regarding drug selection, even to the point of questioning the role of active medications altogether.[63] The best evidence indicates, however, that amide anesthetics with epinephrine provide the greatest efficacy and the longest duration of effect.[64–65]

The third important variable affecting duration is the anesthetic agent itself. The effect of lidocaine without epinephrine is so evanescent in the maxilla that it is not considered a useful agent for pulpal anesthesia. Its moderately high lipid : buffer distribution coefficient cannot overcome the local vasodilation it produces at the injection site. Bupivacaine and etidocaine (Figure 7), on the other hand, are so lipid-soluble that they can provide up to 8 hours of postsurgical pain relief after inferior alveolar nerve block and can reduce the number of oral analgesic doses taken by the patient.[66] This same lipophilicity, however, reduces their usefulness for maxillary pulpal anesthesia, since avid uptake by supraperiosteal tissues hampers diffusion to the superior dental plexus.[67]

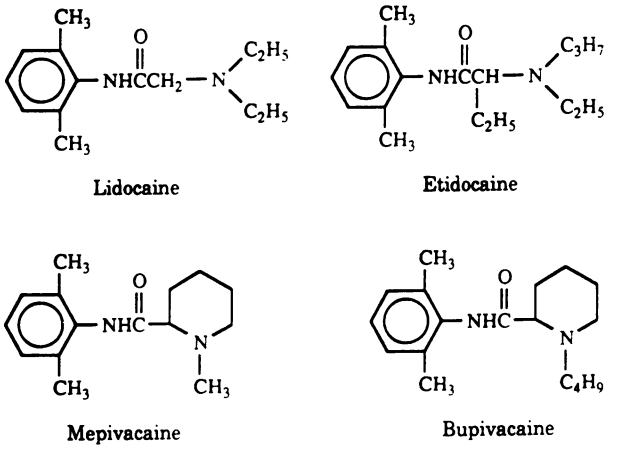


Figure 7. Structures of the amide anesthetics lidocaine and mepivacaine with their respective long-acting congeners etidocaine and bupivacaine.

Dosage Considerations

Most often with young children, but occasionally with adults receiving extensive treatments, dosage limitations for the various clinically available formulations must be considered in drug selection. Table 6 lists maximum dos-

Table 6. Maximum Recommended Doses of Local Anesthetics*

Drug	*Trade name*	*Maximum dose (mg/kg)*	*Maximum adult dose (mg)*
Lidocaine	Alphacaine	4.5†	300
	Lignospan	7.0 (4.5)§	500 (300)
	Lignospan Forte		
	Octocaine		
	Xylocaine		
Mepivacaine	Arestocaine	6.6 (4.5)	400 (300)
	Carbocaine		
	Isocaine		
	Polocaine		
	Scandonest		
Prilocaine	Citanest Plain	8.0 (6.0)	600 (400)
	Citanest Forte		
Bupivacaine	Marcaine	—	225 (90)§
Etidocaine	Duranest	8.0 (5.5)§	400
Propoxycaine /procaine	Ravocaine	6.6§¶	—

*From product information approved by the Food and Drug Administration. Values in parentheses are more conservative guidelines listed in Accepted Dental Therapeutics and/or the USPDI.

†Without vasoconstrictor

§With vasoconstrictor

¶Combined anesthetic weight

age recommendations in product information approved by the Food and Drug Administration and, in parentheses, lower limits found in Accepted Dental Therapeutics[68] and the USP Dispensing Information.[69] Although the dosage limits reported by the manufacturer are presumably based on comparative animal experiments and limited human studies, the more restrictive suggestions appear to have originated with Leonard Monheim,[70] who felt that the generous blood supply to the orofacial region would result in more rapid drug absorption and higher peak blood concentrations than would occur with identical doses administered elsewhere. As yet, this hypothesis has not been tested sufficiently to verify or to refute its validity.

Dosage considerations constrain in particular the use of 3% mepivacaine in small children. With 50% more local anesthetic than 2% mepivacaine with 1 : 20,000 levonordefrin, maximum recommended doses can easily be reached in the young child requiring multiple restorations. Selection of the 3% formulation in an attempt, largely futile, to shorten the duration of mandibular anesthesia and prevent lip and tongue biting, coupled with failure to heed dosage limitations, has proved to be a prescription for disaster.[71] Death and permanent brain injury have also resulted because of a failure to appreciate the additive nature of local anesthetics and other CNS depressants.[72] Small children again are at special risk, because they are often unable to cooperate with dental treatment and therefore are administered deep sedation.

Vasoconstrictor Considerations

Except in situations where there is a desire to limit the duration of maxillary anesthesia, the decision to use a local anesthetic formulation without vasoconstrictor (ie, 3% mepivacaine or 4% prilocaine) is usually made to enhance patient safety. Four groups of patients are at increased risk of adverse reactions to vasoconstrictors: (1) patients hypersensitive to sulfites (discussed previously); (2) patients hyperreactive to adrenergic amines; (3) patients taking drugs that can potentially interact with adrenergic amines; and (4) patients with significant cardiovascular disease.

Some individuals appear to be unusually responsive to vasoconstrictors, especially epinephrine. These patients tend to be highly anxious before injection, however, and it is not clear whether the vasoconstrictor causes the reaction itself or merely augments the effect of endogenously

Table 7. Drug Interactions Involving Local Anesthetics and Vasoconstrictors

Drug	*Interacting drug*	*Effect and recommendation*
Local anesthetics	Alcohol, CNS depressants, opioids, antidepressants, antipsychotics, antihistamines, $MgSO_4$ (parenteral)	Increased CNS and respiratory depression may occur. Use cautiously.
	Antiarrhythmic drugs (eg, quinidine)	Increased cardiac depression may occur. Use cautiously.
	Antimyasthenics (eg, neostigmine)	Local anesthetics may antagonize the effects of antimyasthenic drugs on muscle contractility. Treat patients in consultation with physician.
Amides (eg, lidocaine, mepivacaine)	β-blockers (eg, propranolol), cimetidine	Metabolism of amides in liver is reduced. Use cautiously.
Esters (eg, procaine, propoxycaine)	Anticholinesterases (eg, neostigmine)	Metabolism of esters is reduced. Use cautiously.
	Sulfonamides (eg, sulfisoxazole, trimethoprim–sulfamethoxazole)	Inhibition of sulfonamide action may occur. Avoid concurrent use.
Vasoconstrictors (epinephrine, levonordefrin, norepinephrine)	Inhalation anesthetics (eg, halothane)	Increased possibility of cardiac arrhythmias exists with some agents. Consult with anesthesiologist.
	Tricyclic antidepressants (eg, imipramine, amitriptyline)	Sympathomimetic effects may be enhanced. Use epinephrine cautiously. Avoid levonordefrin and norepinephrine.
	β-blockers (eg, propranolol), adrenergic neuron blockers, (eg, guanethidine)	Hypertensive and/or cardiac reactions are more likely. Use cautiously.
	Phenothiazines (eg, promethazine), butyrophenones (eg, haloperidal)	Vasoconstrictor action is inhibited, which may lead to hypotensive responses. Use cautiously.

Local anesthetics and vasoconstrictors include all formulations available in cartridge form for dental use in the United States. The term "use cautiously" indicates that the interaction is rare and/or not usually dangerous and that careful administration within recommended dosage limits and increased surveillance of drug effects should suffice to avoid serious toxicity.

released hormone. Anxiety, tremulousness, palpitations, and a feeling of chest compression are variably reported. Selecting a formulation without a vasoconstrictor, with lower concentrations of epinephrine, or with levonordefrin in place of epinephrine (which may be less likely to cause symptoms of cardiac stimulation in some patients) may help to minimize this problem, but reducing stress (by limiting the number of procedures planned, and therefore the dosage required) and providing sedation as indicated should also be considered.

Several potentially adverse drug interactions involve the three adrenergic vasoconstrictors used in dental local anesthetics. These are listed in Table 7, along with suggested clinical responses. Although commonly cited in the dental literature, monoamine oxidase inhibitors are excluded because of strong evidence that no interactions occur with exogenously administered epinephrine, levonordefrin, or norepinephrine.[51,73]

The use of epinephrine and related drugs in patients with cardiovascular disease has been debated in dentistry for decades. The marketing of effective anesthetic formulations without vasoconstrictors in the 1960s altered the quality of this debate, and research since then has helped to clarify the pharmacology of adrenergic amines in medically compromised patients. Nevertheless, there is still no simple answer to drug selection. Patients with mild to moderate hypertension that is well controlled by medication should be able to tolerate regular doses of epinephrine; patients with unstable angina pectoris and/or cardiac arrhythmias might be placed at risk from receiving even small amounts of vasoconstrictor. Other sources explore this subject more fully.[51,74] However, a statement made jointly by the American Heart Association and American Dental Association concerning patients with ischemic heart disease provides a good summary[74]: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used."

REFERENCES

1. Liljestrand G: The historical development of local anesthesia. In: Lechat P, ed: International Encyclopedia of Pharmacology and Therapeutics, Sect. 8, Local Anesthetics, vol. 1. New York, Pergamon Press, Ltd., 1971.
2. Fink BR: Leaves and needles: the introduction of surgical local anesthesia. Anesthesiology 1985;63:77–83.
3. Clark JH: History of regional anesthesia. In: Jastak JT, Yagiela JA, eds: Regional Anesthesia of the Oral Cavity. St. Louis, CV Mosby Co., 1981.
4. Strichartz GR, Ritchie JM: The action of local anesthetics on ion channels of excitable tissues. In: Strichartz GR, ed: Local Anesthetics, Handbook of Experimental Pharmacology, vol. 81. Berlin, Springer-Verlag, 1987.
5. Butterworth JF IV, Strichartz GR: Molecular mechanisms of local anesthesia: a review. Anesthesiology 1990;72:711–734.
6. Neumcke B, Schwarz W, Stampfli R: Block of Na channels in the membrane of myelinated nerve by benzocaine. Pflugers Arch 1981;390:230–236.
7. Cahalan MD, Almers W: Interactions between quaternary lidocaine, the sodium channel gates, and tetrodotoxin. Biophys J 1979;27:39–56.
8. Covino BG: Toxicity and systemic effects of local anesthetic agents. In: Strichartz GR, ed: Local Anesthetics, Handbook of Experimental Pharmacology, vol. 81. Berlin, Springer-Verlag, 1987.
9. Courtney KR, Strichartz GR: Structural elements which determine local anesthetic activity. In: Strichartz GR, ed: Local Anesthetics, Handbook of Experimental Pharmacology, vol. 81. Berlin, Springer-Verlag, 1987.
10. de Jong RH: Local Anesthetics, 2nd ed. Springfield, IL, Charles C Thomas, 1977.
11. Gasser HS, Erlanger J: The role of fiber size in the establishment of a nerve block by pressure or cocaine. Am J Physiol 1929;88:581–591.
12. Franz DN, Perry RS: Mechanisms for differential block among single myelinated and nonmyelinated axons by procaine. J Physiol (Lond) 1974;236:193–210.
13. Fink BR: Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. Anesthesiology 1989; 70:851–858.
14. Raymond SA, Steffensen SC, Gugino LD, Strichartz GR: The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg 1989;68:563–570.
15. Haberer J-P, Dalens BJ: Local anesthetics and additives. In: Dalens BJ, ed: Pediatric Regional Anesthesia. Boca Raton, FL, CRC Press, Inc., 1990.
16. Scurlock JE, Meymaris E, Gregus J: The clinical character of local anesthetics: a function of frequency-dependent conduction block. Acta Anaesth Scand 1978;22:601–608.
17. Clarkson CW, Hondeghem LM: Evidence for a specific receptor site for lidocaine, quinidine, and bupivacaine associated with cardiac sodium channels in guinea pig ventricular myocardium. Circ Res 1985;56:496–506.
18. Brown RD: The failure of local anaesthesia in acute inflammation: some recent concepts. Br Dent J 1981;151:47–51.
19. Costa MRC, Catterall WA: Cyclic AMP-dependent phosphorylation of the α subunit of the sodium channel in synaptic nerve ending particles. J Biol Chem 1984;259:8210–8218.
20. Arthur GR: Pharmacokinetics of local anesthetics. In: Strichartz GR, ed: Local Anesthetics, Handbook of Experimental Pharmacology, vol. 81. Berlin, Springer-Verlag, 1987.
21. Benowitz N, Forsyth RP, Melmon KL, Rowland M: Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. Clin Pharmacol Ther 1974;16:87–98.
22. Jorfeldt L, Lewis DH, Löfström JB, Post C: Lung uptake of lidocaine in healthy volunteers. Acta Anaesth Scand 1979; 23:567–574.
23. Tucker GT, Mather LE: Pharmacokinetics of local anaesthetic agents. Br J Anaesth 1975;47:213–224.

24. Tucker GT, Mather LE: Clinical pharmacokinetics of local anaesthetics. Clin Pharmacokinet 1979;4:241–278.

25. Arthur GR, Scott DHT, Boyes RN, Scott DB: Pharmacokinetic and clinical pharmacological studies with mepivacaine and prilocaine. Br J Anaesth 1979;51:481–485.

26. Elvin AT, Cole AFD, Pieper JA, Rolbin SH, Lalka D: Effect of food on lidocaine kinetics: mechanism of food-related alteration in high intrinsic clearance drug elimination. Clin Pharmacol Ther 1981;30:455–460.

27. Feely J, Wade D, McAllister CB, Wilkinson GR, Robertson D: Effect of hypotension on liver blood flow and lidocaine disposition. N Engl J Med 1982;307:866–869.

28. Bax NDS, Tucker GT, Lennard MS, Woods HF: The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. Br J Clin Pharmacol 1985; 19:597–603.

29. Jackson JE, Bentley JB, Glass SJ, Fukui T, Gandolfi AJ, Plachetka JR: Effects of histamine-2 receptor blockade on lidocaine kinetics. Clin Pharmacol Ther 1985;37:544–548.

30. Abernethy DR, Greenblatt DJ: Impairment of lidocaine clearance in elderly male subjects. J Cardiovasc Pharmacol 1983;5:1093–1096.

31. Nation RL, Triggs EJ: Lignocaine kinetics in cardiac patients and aged subjects. Br J Clin Pharmacol 1977;4:439–448.

32. Klein SW, Sutherland RIL, Morch JE: Hemodynamic effects of intravenous lidocaine in man. Can Med Assoc J 1968; 99:472–475.

33. Löfström JB: Physiological effects of local anaesthetics on circulation and respiration. In: Löfström JB, Sjöstrand U, eds: Local Anaesthesia and Regional Blockade, Monographs in Anaesthesiology, vol. 15. Amsterdam, Elsevier Science Publishers BV, 1988.

34. Dowd FJ, Matheny JL: Introduction to cardiovascular pharmacology: antiarrhythmic drugs. In: Neidle EA, Yagiela JA, eds: Pharmacology and Therapeutics for Dentistry 3rd ed. St. Louis, CV Mosby Co., 1989.

35. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–287.

36. Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M: Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;64:1089–1096.

37. Eledjam JJ, de La Coussaye JE, Brugada J, Bassoul B, Gagnol JP, Febregat JR, Massé C, Sassine A: In vitro study on mechanisms of bupivacaine-induced depression of myocardial contractility. Anesth Analg 1989;69:732–735.

38. Thomas RD, Behbehani MM, Coyle DE, Denson DD: Cardiovascular toxicity of local anesthetics: an alternative hypothesis. Anesth Analg 1986;65:444–450.

39. Heavner JE: Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle of cats. Anesth Analg 1986;65:133–138.

40. Holroyd SV, Requa-Clark B: Local anesthetics. In: Holroyd SV, Wynn RL, eds: Clinical Pharmacology in Dental Practice, 3rd ed. St. Louis, CV Mosby Co., 1983.

41. Goldstein DS, Dionne R, Sweet J, Gracely R, Brewer HB Jr, Gregg R, Keiser HR: Circulatory, plasma catecholamine, cortisol, lipid, and psychological responses to a real-life stress (third molar extractions): effects of diazepam sedation and inclusion of epinephrine with the local anesthetic. Psychosomat Med 1982;44:259–272.

42. Chernow B, Balestrieri F, Ferguson CD, Terezhalmy GT, Fletcher JR, Lake CR: Local dental anesthesia with epinephrine. Arch Intern Med 1983;143:2141–2143.

43. Dionne RA, Goldstein DS, Wirdzek PR: Effects of diazepam premedication and epinephrine-containing local anesthetic on cardiovascular and plasma catecholamine responses to oral surgery. Anesth Analg 1984;63:640–646.

44. Cioffi GA, Chernow B, Glahn RP, Terezhalmy GT, Lake CR: The hemodynamic and plasma catecholamine responses to routine restorative dental care. J Am Dent Assoc 1985;111: 67–70.

45. Troullos ES, Goldstein DS, Hargreaves KM, Dionne RA: Plasma epinephrine levels and cardiovascular response to high administered doses of epinephrine in local anesthesia. Anesth Prog 1987;34:10–13.

46. Knoll-Köhler E, Frie A, Becker J, Ohlendorf D: Changes in plasma epinephrine concentrations after dental infiltration anesthesia with different doses of epinephrine. J Dent Res 1989;68:1098–1101.

47. Cryer PE: Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N Engl J Med 1980;303:436–444.

48. Kennedy WF Jr, Bonica JJ, Ward RJ, Tolas AG, Martin WE, Grinstein A: Cardiorespiratory effects of epinephrine when used in regional anesthesia. Acta Anaesthesiol Scand Suppl 1966;23:320–333.

49. Kaneko Y, Ichinohe T, Sakurai M, Sakurai M, Nakakuki T: Relationship between changes in circulation due to epinephrine oral injection and its plasma concentration. Anesth Prog 1989;36:188–190.

50. Kiyomitsu Y, Sugiyama K, Joh S: The effects of catecholamines added to lidocaine on cardiac function. Anesth Prog 1989;36:198–200.

51. Jastak JT, Yagiela JA: Vasoconstrictors and local anesthesia: a review and rationale for use. J Am Dent Assoc 1983; 107:623–630.

52. Minasian A, Yagiela JA: The use of amide local anesthetics in patients susceptible to malignant hyperthermia. Oral Surg Oral Med Oral Pathol 1988;66:405–15.

53. Yagiela JA, Benoit PW, Buoncristiani RD, Peters MP, Fort NF: Comparison of the myotoxic effects of lidocaine with epinephrine in rats and humans. Anesth Analg 1981;60:471–480.

54. Ludwig SC: Acute toxic methemoglobinemia following dental analgesia. Ann Emerg Med 1981;10:265–266.

55. Spielman FJ, Anderson JA, Terry WC: Benzocaine-induced methemoglobinemia during general anesthesia. J Oral Maxillofac Surg 1984;42:740–743.

56. Cassuto J, Nellgård P, Stage L, Jönsson A: Amide local anesthetics reduce albumin extravasation in burn injuries. Anesthesiology 1990;72:302–307.

57. Borg T, Modig J: Potential anti-thrombotic effects of local anaesthetics due to their inhibition of platelet aggregation. Acta Anaesthesiol Scand 1985;29:739–742.

58. Abraham ZA, Lees DE: Two cardiac arrests after needle

punctures in a patient with mitral valve prolapse: psychogenic? Anesth Analg 1989;69:126–128.

59. Schwartz HJ, Sher TH: Bisulfite sensitivity manifesting as allergy to local dental anesthesia. J Allergy Clin Immunol 1985;75:525–527.

60. Simon RA: Sulfite sensitivity. Ann Allergy 1986;56:281–288.

61. Yagiela JA: Local anesthetics: a century of progress. Anesth Prog 1989;32:47–56.

62. Astra standard times: average duration of pulpal anesthesia. Westborough, MA, Astra® Pharmaceutical Products, Inc., 1989.

63. Handler LE, Albers DD: The effects of the vasoconstrictor epinephrine on the duration of pulpal anesthesia using the intraligamentary injection. J Am Dent Assoc 1987;114:807–809.

64. Kaufman E, LeResche L, Sommers E, Dworkin SF, Truelove EL: Intraligamentary anesthesia: a double-blind comparative study. J Am Dent Assoc 1984;108:175–178.

65. Edwards RW, Head TW: A clinical trial of intraligamentary anesthesia. J Dent Res 1989;68:1210–1214.

66. Danielsson K, Evers H, Holmlund A, Kjellman O, Nordenram Å, Persson N-E: Long-acting local anaesthetics in oral surgery: clinical evaluation of bupivacaine and etidocaine for mandibular nerve block. Int J Oral Maxillofac Surg 1986;15:119–126.

67. Danielsson K, Evers H, Nordenram Å: Long-acting local anesthetics in oral surgery: an experimental evaluation of bupivacaine and etidocaine for oral infiltration anesthesia. Anesth Prog 1985;32:65–68.

68. Council on Dental Therapeutics of the American Dental Association: Accepted Dental Therapeutics, 40th ed. Chicago, American Dental Association, 1984.

69. USP Dispensing Information, 10th ed. Rockville, MD, United States Pharmacopeial Convention, Inc., 1990.

70. Monheim LM: Local Anesthesia and Pain Control in Dental Practice, 4th ed. St. Louis, CV Mosby Co., 1969.

71. Berquist HC: The danger of mepivacaine 3% toxicity in children. J Calif Dent Assoc 1975;3:13.

72. Goodson JM, Moore PA: Life-threatening reactions after pedodontic sedation: an assessment of narcotic, local anesthetic, and antiemetic drug interaction. J Am Dent Assoc 1983;107:239–245.

73. Cassidy JP, Phero JC, Grau WH: Epinephrine: systemic effects and varying concentrations in local anesthesia. Anesth Prog 1986;33:289–297.

74. Kaplan EL, ed: Cardiovascular Disease in Dental Practice. Dallas, American Heart Association, 1986.