Pharmacology of Local Anesthetics Used in Oral Surgery

Joseph A. Giovannitti Jr, DMDa,*, Morton B. Rosenberg, DMDb,c, James C. Phero, DMDd

INTRODUCTION

The ability to provide safe, effective local anesthesia is the cornerstone of clinical oral surgical practice. Like any regional anesthetic technique, the use and effectiveness depend on patient considerations, the extent and duration of the procedure, choice of drug and technique, and the skill and experience of the practitioner. Every clinician should be aware of his or her skill limitations, and the limitations of the contemplated technique and agent. These factors must be clearly understood preoperatively to enhance the chance of success. The administration of local anesthetics is often complicated by the existence of multifactorial psychological considerations associated with the delivery of dental care. It is imperative for health care professionals to understand and appreciate these issues to properly implement perioperative behavioral or pharmacologic management strategies to reduce fear and anxiety to acceptable levels. These considerations are discussed elsewhere in this issue. This article focuses on the pharmacology and clinical application of local anesthetics used in dentistry. A thorough knowledge of these agents gives the surgeon the ability to individualize care to meet the specific surgical and anesthetic needs of the patient. A discussion of the anatomy and routine injection techniques is not included in this article because it is assumed that the reader already has an expert’s command of these subjects.

KEYWORDS

- Local anesthetics
- Pharmacology
- Complications and reasons for failure
- Future trends

KEY POINTS

- Local anesthesia remains the foundation of pain control in dentistry especially when combined with moderate-deep sedation for invasive and painful procedures in the contemporary oral and maxillofacial surgical model.
- Local anesthetics remain the safest and most effective drugs in medicine and dentistry to relieve intraoperative and postoperative pain.
- It is only with a thorough understanding of pharmacology and anatomy that clinicians have the basic clinical foundation to enhance the care of patients.

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medical history with special emphasis on past anesthetic experiences, a focused physical examination, determination of physical risk, and the potential for adverse drug interactions. The patient’s weight and body mass index are also important considerations. Without this information and practitioner knowledge base, a reasonable and rational anesthesia plan cannot be successfully formulated.

HISTORY

The next major advance in pain control, after the introduction of inhaled nitrous oxide and ether, was the isolation of cocaine by Niemann in 1859. At the suggestion of Sigmund Freud, Karl Koller began using topical cocaine for ophthalmologic procedures in 1884. In that same year, the famous surgeon William Halstead began his experiments with the application of cocaine to peripheral nerves to produce a conduction blockade. Using the newly available hypodermic needle and syringe, he performed the first peripheral nerve block, successfully anesthetizing the inferior alveolar nerve. It was apparent that cocaine-induced anesthesia was short acting, so Corning actually advocated the use of a tourniquet to retard the absorption of the drug and prolong the effect. In 1903, Heinrich Braun suggested the addition of epinephrine to act as a “chemical” tourniquet to prolong duration. Because of the transient effect of cocaine and its addictive potential, the search was intensified for a more effective and less toxic anesthetic. Alfred Einhorn introduced a cocaine analog, procaine, in 1904. Procaine remained the sole local anesthetic in dentistry until 1948, when lidocaine was introduced by Nils Lofgren. Lidocaine is an aminoamide local anesthetic with improved efficacy and duration, and less toxicity than procaine. It has become the gold standard for local anesthetics in dentistry against which all others are compared. Other amide local anesthetics followed: mepivacaine in 1960, prilocaine in 1965, bupivicaine in 1983, and articaine in 2000.

Another major event in the history of local anesthesia in dentistry was the invention of the dental syringe and cartridge by Harvey Cook in 1920. Before this development, powdered local anesthetics had to be mixed in solution and then drawn into a syringe for administration. An Army medic, Cook based his design on the bolt-action rifle and cartridges in use during World War I. Later, his Cook-Waite laboratories developed the disposable sterile needle, which reduced infection and needle breakage. A review of historical developments in local anesthesia is found in Table 1.

PHARMACOLOGY

Local anesthetics reversibly block conduction along a nerve distal to the site of application. They are generally classified according to their chemical structure, rate of onset, potency, and duration of action. Chemically, they are either aminoesters or aminoamides (ie, an aromatic, lipophilic ring connected to a hydrophilic amine group by an intermediate chain containing either an ester or amide linkage) (Fig. 1). Ester local anesthetics are not available in dental cartridges primarily because of lack of efficacy, the potential

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Table 1

<table>
<thead>
<tr>
<th>Individual/ Company</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1859 Niemann</td>
<td>Isolation of cocaine</td>
</tr>
<tr>
<td>1884 Koller</td>
<td>Cocaine topical anesthesia</td>
</tr>
<tr>
<td>1884 Halstead</td>
<td>Cocaine regional anesthesia</td>
</tr>
<tr>
<td>1885 Corning</td>
<td>Tourniquet to retard absorption</td>
</tr>
<tr>
<td>1903 Braun</td>
<td>Epinephrine as a chemical tourniquet</td>
</tr>
<tr>
<td>1904 Einhorn</td>
<td>Synthesis of procaine</td>
</tr>
<tr>
<td>1905 Braun</td>
<td>Clinical use of procaine</td>
</tr>
<tr>
<td>1920 Cook Laboratories</td>
<td>Anesthetic syringe and cartridge</td>
</tr>
<tr>
<td>1943 Lofgren</td>
<td>Synthesis of lidocaine</td>
</tr>
<tr>
<td>1947 Novocol</td>
<td>Dental aspirating syringe</td>
</tr>
<tr>
<td>1948 Astra</td>
<td>Lidocaine for dentistry</td>
</tr>
<tr>
<td>1959 Cook-Waite</td>
<td>Sterile disposable needle</td>
</tr>
</tbody>
</table>

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Fig. 1. Lidocaine is the prototypical aminoamide. Procaine is the prototypical aminoester.
for allergenicity, and the advantages of newer aminoamides.

**Mechanism of Action**

Normal depolarization causes conformational changes in the nerve membrane that allow for the passage of sodium ions through specified channels resulting in the propagation of the action potential along the nerve. Local anesthetics bind to specific sites within the sodium channels, preventing these conformational changes, and thus impair conduction. As more receptors are occupied, there is a progressive reduction in the rate and degree of depolarization until conduction fails.

Franz and Perry\(^1\) noted that nerve conduction was disrupted when a critical length of the nerve was exposed to a local anesthetic. The size of the nerve fiber was not a factor. However, because conduction along myelinated nerves occurs from one node of Ranvier to another (ie, saltatory conduction), a longer critical length is required for exposure to local anesthetics for a block to occur. This results in a differential sensitivity of nerve fibers to the effects of local anesthetics based on their size. Because larger-diameter myelinated fibers have a greater internodal distance than smaller myelinated fibers, there is a differential sensitivity to the effects of local anesthetics based on the diameter of the nerve fiber. Smaller nerve fibers, either myelinated or unmyelinated, typically transmit pain and proprioceptive impulses, whereas larger myelinated fibers carry motor impulses. Thus, when local anesthetics are applied to a nerve trunk, there is a sequence of disappearance of sensations based on the differential sensitivity of the nerves involved. Typically, pain fibers are blocked first, followed by temperature, touch, pressure, and motor function.

The differential sensitivity of nerves to local anesthetics is also influenced by the frequency of impulses along the nerve fiber. Higher-frequency impulses make more sodium channels available to exposure by local anesthetics, and these fibers are blocked faster than slower frequency fibers. This is known as use-dependent block, and is clinically significant in that pain impulses are of higher frequency than motor impulses. Thus, pain impulses are blocked preferentially and more rapidly.

Clinical onset and recovery characteristics are determined by the organization of nerve trunks themselves. Because the local anesthetic diffuses through the nerve bundle, the outer or mantle axons are affected first. Because the drug diffuses into the core, the structures innervated by these axons are affected later. In the case of the inferior alveolar nerve, proximal structures are innervated by the mantle fibers and distal structures are innervated by the core. The onset of an inferior alveolar nerve block is therefore proximal to distal, molars to incisors and lower lip. Recovery is also proximal to distal, with the lip being the last to recover from the block.

**Ionization**

The degree of ionization after a local anesthetic is injected determines its rate of onset. After the acidic local anesthetic solution is injected it is buffered by the body and dissociates into an uncharged base and a cationic form. The uncharged base form diffuses through the nerve membrane. The amount of base form depends on the pKa of the local anesthetic and the pH of the tissue. The closer the anesthetic’s pKa is to the tissue pH, the more base form is available for diffusion, resulting in a faster onset. Local anesthetics with the lowest pKa values have the fastest rate of onset (Table 2). When inflammation is present, tissue pH becomes more acidic and local anesthesia is more difficult to achieve.

**Lipid Solubility and Protein Binding**

The aromatic ring of the local anesthetic molecule determines its lipid solubility. Because nerve membranes are primarily lipid, the drugs with the greatest lipid affinity demonstrate the greatest potency. The protein-binding properties of local anesthetics determine their duration of action. Sodium channels and receptor sites are largely protein and highly protein-bound molecules attach securely to the active site. Additionally, protein binding creates a reservoir of drug that can be made available as the unbound drug is removed from the active site by vascular uptake. A higher percentage of protein binding means a longer duration of action (Table 3).

**Systemic Effects**

Local anesthetics impair conduction in all neural tissues at the site of injection, but with particular

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKa</th>
<th>% Base Form at pH 7.4</th>
<th>Onset of Action (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivacaine</td>
<td>7.7</td>
<td>33</td>
<td>2–4</td>
</tr>
<tr>
<td>Articaine</td>
<td>7.8</td>
<td>29</td>
<td>2–4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.9</td>
<td>25</td>
<td>2–4</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.9</td>
<td>25</td>
<td>2–4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>17</td>
<td>5–8</td>
</tr>
</tbody>
</table>
affinity for those in the cardiovascular and central nervous systems. In the central nervous system, neuronal excitation occurs as local anesthetic concentrations rise rapidly. This is counterintuitive because local anesthetics block conduction. It is postulated that inhibitory pathways are affected first, allowing excitatory pathways to manifest themselves. Local anesthetics are also known to affect potassium channels, which may in itself produce neural excitation.1 Patients may experience agitation, disorientation, dizziness, tinnitus, involuntary muscle activity, or frank seizures when local anesthetics are given higher than maximum recommended doses or injected directly into the vasculature.

All local anesthetics inhibit cardiac conduction. In therapeutic doses lidocaine prolongs the refractory period in the myocardial conduction system and is useful in preventing or controlling ventricular dysrhythmias. In toxic doses, local anesthetics diminish myocardial contractility and conduction resulting in reduced cardiac output and systemic hypotension. Cardiovascular system collapse is the end result of local anesthetic-induced cardiac toxicity.

Although hypoxia associated with seizure activity likely contributes to the cardiac toxicity of other local anesthetics, bupivacaine is known to be directly cardiotoxic. The high lipid solubility of bupivacaine compared with other local anesthetics contributes to its increased potential for cardiac toxicity. Additionally, bupivacaine preparations contain dextrorotatory and levorotatory enantiomers. Cardiac toxicity is primarily associated with the dextrorotatory enantiomer.3 The inhibition of myocardial potassium channels also contributes to its toxicity. In obstetric anesthesia it is known that high concentrations or volumes of systemic bupivacaine can cause instantaneous cardiovascular system collapse that is resistant to usual resuscitative measures. Methods for the reversal of this complication are discussed later in this article. Fortunately, the doses of bupivacaine used in dentistry are far below that of other medical major nerve blocks, making this type of cardiac toxicity highly unlikely.

Finally, local anesthetics have varying effects on the peripheral vasculature. Most local anesthetics are vasodilators to varying degrees. Lidocaine, bupivacaine, and articaine are combined with epinephrine to enhance the duration and efficacy of the nerve block, whereas mepivacaine, prilocaine, and ropivacaine are not as profound vasodilators and may be used as plain solutions. Cocaine is unique in that it causes vasoconstriction by inhibiting the reuptake of norepinephrine into the adrenergic nerve end plates. For this reason, cocaine potentiates the effects of added vasoconstrictors and may produce a severe drug interaction leading to malignant hypertension, stroke, myocardial infarction, and death. Because of these profound vasoconstrictor effects and other associated issues, injectable cocaine preparations are not used in dentistry.

### Metabolism and Excretion

Ester local anesthetics are hydrolyzed in the plasma by pseudocholinesterase into para-aminobenzoic acid and other derivatives. These derivatives undergo further biodegradation in the liver, and a small amount of the drug is eliminated unchanged. Patients with pseudocholinesterase deficiencies are at an increased risk for toxicity from ester local anesthetics. Para-aminobenzoic acid has allergic potential and has been implicated in the development of allergic reactions to esters, such as procaine and tetracaine, and to amide solutions containing methylparaben as an antimicrobial. At this point in time, there are no commercially available ester local anesthetics in dental cartridges. Local anesthetics available in dental cartridges are paraben-free, and paraben-free amides are also available in single- or multiple-dose vials. The practitioner must be aware, however, that many multiple-dose vials do contain methylparaben. Bisulfites are also found in local anesthetic solutions containing epinephrine and act as an antioxidant and preservative. When considering allergy testing for local anesthetics, methylparaben and bisulfite free solutions must be used for accurate interpretation.

Amide local anesthetics are metabolized in the liver primarily by CYP3A4 and CYP1A2 isoforms.4 The rate of metabolism depends on liver blood flow and liver function, so conditions that slow liver blood flow can retard the metabolism of amides and have the potential for increased toxicity. Although still classified as amide, articaine, by virtue of its ester side-chain, undergoes partial hydrolysis by nonspecific plasma esterases and liver metabolism. Its resultant 25-minute half-life is much shorter than other amide local anesthetics, thus reducing its toxic potential. Pseudocholinesterase deficiency does not add to the toxicity of articaine.
Certain metabolites of local anesthetics may have activity unrelated to their clinical intent. Monoethylglycinexylidide, a metabolite of lidocaine, may produce sedation and drowsiness after lidocaine administration. Ortho-toluidine, a metabolite of prilocaine, has been implicated in the development of methemoglobinemia.

LOCAL ANESTHETICS

Although any available local anesthetic solution acceptable for neural blockade in other parts of the body may be used for regional anesthesia of the head and neck, only five agents are currently available in cartridge form for dentistry (Table 4). As in other types of neural blockade, the choice of anesthetic agent, amount, type, and concentration of vasoconstrictor is based on many factors, such as physical status, age and weight of the patient, duration of the procedure, the need for hemostasis, and practitioner bias. Local anesthesia toxicity is a concern where large volumes of concentrated local anesthetic are used. Toxicity is avoided by using the lowest concentration of local anesthetic that produces the required block, calculating the maximum volume of solution that each patient may receive in advance of the injection, injecting slowly, and always aspirating before injection. This is especially true in the pediatric, severely compromised, and geriatric patients where drug toxicity can become a life-threatening complication if maximum doses are not strictly adhered (Table 5).

Local anesthetics are supplied in single-dose glass cartridges containing either 1.7 or 1.8 mL, depending on the origin of manufacture. Cartridges manufactured in Canada and Europe contain 1.7 mL of solution, whereas cartridges manufactured in the United States contain 1.8 mL of solution. This discrepancy matters little in determining the ultimate dose administered, and traditionally the 1.8-mL volume is used to calculate the administered dose and the maximum recommended dose. Cartridges of a plain local anesthetic solution contain the hydrochloride salt of the local anesthetic and distilled water. Cartridges containing a vasoconstrictor also contain epinephrine or levonordefrin, sodium metabisulfite, and citric acid. These latter act to stabilize the vasoconstrictor and prevent oxidative breakdown.

Table 4
Local anesthetics available in dental cartridges

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>1:50,000 epinephrine</td>
</tr>
<tr>
<td></td>
<td>1:100,000 epinephrine</td>
</tr>
<tr>
<td>Mepivacaine 3%</td>
<td>Plain (no vasoconstrictor)</td>
</tr>
<tr>
<td>Mepivacaine 2%</td>
<td>1:20,000 levonordefrin</td>
</tr>
<tr>
<td>Prilocaine 4%</td>
<td>Plain</td>
</tr>
<tr>
<td></td>
<td>1:200,000 epinephrine</td>
</tr>
<tr>
<td>Articaine 4%</td>
<td>1:100,000 epinephrine</td>
</tr>
<tr>
<td></td>
<td>1:200,000 epinephrine</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>1:200,000 epinephrine</td>
</tr>
</tbody>
</table>

Lidocaine

Lidocaine is the most commonly used dental local anesthetic in the United States, and has become the gold standard against which all other dental local anesthetics are compared. Although lidocaine is supplied in dental cartridges as a 2% plain solution, it is rarely used because of its relative ineffectiveness and short duration. Lidocaine 2% combined with a vasoconstrictor in a 1:100,000 concentration provides reliable and profound pulpal anesthesia for approximately 60 minutes with a duration of soft tissue anesthesia ranging from 3 to 5 hours. Lidocaine is also supplied as a 2% solution with 1:50,000 epinephrine. Although this concentration may be useful to provide surgical hemostasis by local infiltration, its routine use for primary operative or surgical anesthesia should be avoided because of the possibility of an acute epinephrine reaction, which may often manifest as hypertension or tachycardia in susceptible patients.

Mepivacaine

Mepivacaine is very similar to lidocaine in its efficacy, onset, and duration. It is supplied in dental cartridges as a 2% solution with 1:20,000 levonordefrin and as a 3% plain solution. It is effective as a plain solution because of its weaker vasodilator properties. This gives the plain solution practical use for short-duration procedures or for use in patients where vasoconstrictors would be contraindicated. Mepivacaine 3% plain solution is a popular alternative for patients in whom epinephrine may be contraindicated.

Prilocaine

Prilocaine is somewhat less potent than lidocaine and so is supplied in a higher concentration. It is available as a plain 4% solution, or as a 4% solution with 1:200,000 epinephrine. It is similar in duration and efficacy as lidocaine and its plain and lowered concentration of vasoconstrictor are useful for procedures of short duration or when the amount of vasoconstrictor should be minimized. Prilocaine has been implicated in a higher incidence of paresthesia associated with nerve
block injections compared with lidocaine. Its potential to induce methemoglobinemia also may limit its use.

Articaine

Articaine is the newest local anesthetic available in dental cartridges, introduced in 1976 in Europe and in 2000 in the United States. Articaine with epinephrine has a similar clinical profile as lidocaine, mepivacaine, and prilocaine with vasoconstrictors. It is available in dental cartridges as a 4% solution containing either epinephrine in 1:100,000 or 1:200,000 concentrations. The lower concentration of epinephrine is useful when the total amount of vasoconstrictor should be reduced. A major advantage of articaine is that its half-life is significantly reduced because of hydrolysis of its ester side-chain by nonspecific plasma esterases. This reduces its toxic potential. Its 4% concentration has been implicated as a causative factor in the development of paresthesia after nerve block injections. Articaine seems to be more effective for infiltration techniques in the maxilla and mandible than other local anesthetics.

Bupivacaine

Bupivacaine is similar chemically to mepivacaine, but is much more lipid soluble and thus more potent. It is much more cardiotoxic than other local

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Weight (kg)</th>
<th>Lidocaine</th>
<th>Articaine a</th>
<th>Mepivacaine</th>
<th>Mepivacaine</th>
<th>Prilocaine</th>
<th>Bupivacaine b</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% 1:100,000 epinephrine</td>
<td>1% 1:100,000 or 1:200,000 epinephrine</td>
<td>3% Plain</td>
<td>2% 1:20,000 levonordefrin</td>
<td>4% Plain</td>
<td>0.5% 1:100,000 epinephrine</td>
<td>4% 1:100,000 epinephrine</td>
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</tr>
<tr>
<td>10</td>
<td>22</td>
<td>1.9</td>
<td>NR</td>
<td>1.2</td>
<td>1.8</td>
<td>1.1</td>
<td>NR</td>
</tr>
<tr>
<td>15</td>
<td>33</td>
<td>2.9</td>
<td>NR</td>
<td>1.8</td>
<td>2.8</td>
<td>1.7</td>
<td>NR</td>
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<tr>
<td>20</td>
<td>44</td>
<td>3.9</td>
<td>NR</td>
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<td>2.2</td>
<td>NR</td>
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<tr>
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<td>4.9</td>
<td>2.4</td>
<td>3.1</td>
<td>4.6</td>
<td>2.8</td>
<td>NR</td>
</tr>
<tr>
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<td>66</td>
<td>5.8</td>
<td>2.9</td>
<td>3.7</td>
<td>5.5</td>
<td>3.3</td>
<td>NR</td>
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<tr>
<td>35</td>
<td>77</td>
<td>6.8</td>
<td>3.4</td>
<td>4.3</td>
<td>6.4</td>
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<td>NR</td>
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<tr>
<td>40</td>
<td>88</td>
<td>7.8</td>
<td>3.9</td>
<td>4.9</td>
<td>7.3</td>
<td>4.4</td>
<td>NR</td>
</tr>
<tr>
<td>45</td>
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<td>8.8</td>
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<td>5.5</td>
<td>8.3</td>
<td>5.0</td>
<td>6.6</td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>9.7</td>
<td>4.9</td>
<td>6.1</td>
<td>9.2</td>
<td>5.6</td>
<td>7.3</td>
</tr>
<tr>
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<td>121</td>
<td>10.7</td>
<td>5.3</td>
<td>6.7</td>
<td>10.1</td>
<td>6.1</td>
<td>8.1</td>
</tr>
<tr>
<td>60</td>
<td>132</td>
<td>11.1</td>
<td>5.8</td>
<td>7.3</td>
<td>11.0</td>
<td>6.7</td>
<td>8.8</td>
</tr>
<tr>
<td>65</td>
<td>143</td>
<td>11.1</td>
<td>6.3</td>
<td>7.4</td>
<td>11.1</td>
<td>7.2</td>
<td>9.5</td>
</tr>
<tr>
<td>&gt;70</td>
<td>≥154</td>
<td>11.1</td>
<td>6.9</td>
<td>7.4</td>
<td>11.1</td>
<td>8.3</td>
<td>10.0</td>
</tr>
</tbody>
</table>

**Table 5**

Maximum local anesthetic dose for adult and pediatric patients (based on weight)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cartridges/10 kg</th>
<th>Maximum Cartridges</th>
<th>Maximum Cartridges for the Cardiovascular-impaired Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% Lidocaine 1:100,000 epinephrine</td>
<td>2</td>
<td>11.1</td>
<td>1–2</td>
</tr>
<tr>
<td>4% Articaine 1:100,000 epinephrine</td>
<td>1</td>
<td>6.9</td>
<td>1–2</td>
</tr>
<tr>
<td>4% Articaine 1:200,000 epinephrine</td>
<td>1</td>
<td>6.9</td>
<td>2–4</td>
</tr>
<tr>
<td>3% Mepivacaine plain</td>
<td>1.2</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>2% Mepivacaine 1:20,000 levonordefrin</td>
<td>1.8</td>
<td>11.1</td>
<td>1–2</td>
</tr>
<tr>
<td>4% Prilocaine plain</td>
<td>1.1</td>
<td>8.3</td>
<td>7.8</td>
</tr>
<tr>
<td>4% Prilocaine 1:200,000 epinephrine</td>
<td>1.1</td>
<td>8.3</td>
<td>2–4</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not recommended.

a Articaine is not recommended for children younger than 4 years old.

b Bupivacaine is not recommended for children younger than 12 years old.
Local Anesthetics Used in Oral Surgery

anesthetics because of the activity of its dextrorotary enantiomer on cardiac tissue. Its pKa value is much higher than other drugs in this class, resulting in a clinically significant slower onset time. Its high lipid solubility renders it unsuitable for maxillary infiltration injection because its diffusion is retarded by sequestration in mucosal tissues. Bupivacaine is available in dental cartridges as a 0.5% solution with 1:200,000 epinephrine. Bupivacaine is primarily used in dentistry to produce long-acting soft tissue anesthesia lasting 8 hours or more after oral surgical procedures. Combined with appropriate postoperative analgesics and anti-inflammatory drugs, bupivacaine plays an important role in reducing pain in the postoperative period.

**VASOCONSTRICTORS**

Vasoconstrictors are used to prolong the duration of anesthetic effect, decrease the rate of absorption of local anesthetics, and decrease localized bleeding at the site of administration. Profound α-adrenergic agonism significantly reduces blood flow at the injection site, causing retention of the local anesthetic in the vicinity of the neuronal tissue. The most pronounced effect is to increase the duration of intermediate-acting local anesthetics in the maxilla and mandible.

The two vasoconstrictors available in dental cartridges are epinephrine and levonordefrin. Epinephrine is available in three concentrations: (1) 5 μg/mL (1:200,000); (2) 10 μg/mL (1:100,000); and (3) 20 μg/mL (1:50,000). A standard dental cartridge with 1:100,000 epinephrine contains 18 μg of epinephrine. Levonordefrin is found only in dental cartridges containing mepivacaine in a concentration of 50 μg/mL (1:20,000). A standard dental cartridge with 1:20,000 levonordefrin contains 90 μg of levonordefrin. Although levonordefrin is a weaker α-adrenergic agonist than epinephrine, the 1:20,000 concentration is five times greater than the standard concentration of epinephrine. Levonordefrin also has a preponderance of α-adrenergic effects relative to its β-adrenergic stimulation. This could create a potential drug interaction resulting in significant hypertension when administered to patients taking nonselective β-blocking drugs.9 The mucosa of the oral cavity is highly vascularized, and the systemic uptake of vasoconstrictors following intraoral injection may be rapid. A single dental cartridge of lidocaine 2% with 1:100,000 epinephrine can double the resting epinephrine titer within minutes.10,11 Furthermore, the intraoral administration of eight dental cartridges of a 1:100,000 epinephrine solution may produce plasma epinephrine concentrations equivalent to those present during heavy exercise.12 Sung and colleagues13 demonstrated that a slow infusion of epinephrine produced a significant incidence of chest pain and ST-segment depression in patients with coronary artery disease. It is therefore important to limit the amount of vasoconstrictor-containing local anesthetic solutions in patients with severe anxiety or cardiovascular disease. As a general rule, the minimum possible amount of vasoconstrictor should be used. Caution should also be exercised in patients taking nonspecific β-adrenergic blockers, adrenergic neuron blockers, tricyclic antidepressants, phenothiazine derivatives, and cocaine.

**USE IN PEDIATRICS**

Local anesthetics are important in the dental care of children and are safe and effective. However, pediatric patients are easily susceptible to local anesthetic toxicity if care is not taken to calculate the correct dosage before administration. All children and small adults should be weighed before establishing the maximum amount of local anesthetic that can be administered safely. Calculations of the maximum recommended local anesthetic dose are based on weight and patient acuity. Although some authors14 have made no dose modifications on a milligram per kilogram basis, the American Academy of Pediatric Dentistry has developed a Guideline on Use of Local Anesthetics for Pediatric Dental Patients with dosage recommendations for the safe use of local anesthetics in pediatric patients.15 Specifically, the dosages of lidocaine and mepivacaine have been significantly reduced compared with the recommended adult doses. The maximum recommended dose of these two drugs is 4.4 mg/kg. Thus, for a 20-kg child, the maximum dose of lidocaine is 88 mg, or 2.4 cartridges of the drug. Articaine, which has a lower toxic potential, may be given in a dose up to 7 mg/kg. The same 20-kg child could therefore receive 140 mg, or 1.9 cartridges of articaine. Bupivacaine is not used in the pediatric patient because of the prolonged duration of action and the potential for self-mutilation.

Although lip and cheek biting might be minimized by the administration of phentolamine mesylate (OraVerse; Novalor Pharmaceuticals, San Diego, CA) at the end of a procedure, this may not be practical for oral surgical procedures in which the rapid onset of postoperative pain is a major concern, but could be of use in the pediatric or special needs patient.

In a landmark paper, Goodson and Moore16 demonstrated that life-threatening toxic local anesthetic reactions occurred with higher frequency
in pediatric patients undergoing sedation that included opioids. Care should be taken during pediatric sedation to use the minimally effective dose of opioid and local anesthetic. The use of oral midazolam as a premedicant combined with nitrous oxide–oxygen is a viable sedation technique, as is the use of short-acting opioids, such as remifentanil.

COMPLICATIONS AND REASONS FOR FAILURE

Paresthesia

One of the most devastating localized complications after any intraoral injection is the occurrence of prolonged paresthesia in any of the trigeminal nerve distributions. Most typically it is associated with the inferior alveolar and especially lingual nerves, and may result from direct mechanical needle trauma, hemorrhage, extraneural or intra-neural edema, or chemical neurotoxicity of the local anesthetic drug itself. The altered sensation is usually transient and resolves spontaneously within days, weeks, or months. In rare instances, the damage can be of long duration or permanent. Haas and Lennon conducted a long-term retrospective study examining the incidence of paresthesia associated with local anesthesia. They reported that paresthesia was more frequent with 4% prilocaine and 4% articaine relative to the frequency of use. They reported an incidence of 1 in 500,000 for prilocaine and articaine, and an incidence of 1 in 1.2 million for other local anesthetics. Although it is possible that the drugs themselves could be neurotoxic, it seems more likely that the 4% concentration is the determining factor. The surgeon should carefully weigh the benefit/risk ratio when considering the use of articaine or any other 4% local anesthetic solution for a mandibular block injection.

Muscle Trismus

Muscle trismus can also be a sequela of a mandibular block. Limitation of muscular function after an intraoral injection may be caused by hematoma formation, direct muscle injury secondary to needle trauma, localized muscle necrosis secondary to the anesthetic drug or vasoconstrictor, infection in a fascial space, or the introduction of a foreign body. The treatment of intraoral trismus may include nonsteroidal anti-inflammatory agents, saline mouth rinses, antibiotics, and physical therapy.

Hematoma

Formation of a hematoma is the result of direct needle trauma to a blood vessel, and is most likely to occur after a posterior superior alveolar nerve block and greater palatine canal and high tuberosity approaches to the maxillary nerve. Signs and symptoms of hematoma include rapid swelling, a sensation of fullness in the area, facial asymmetry, and mild trismus. Management of a hematoma includes patient reassurance and application of ice to the affected area on the day of injury, followed in 24 hours by application of heat. When indicated, posttreatment antibiotics may also be necessary.

Mucosal Irritation

This may be produced by several different causes. Topical anesthetics, when applied to the mucosa for extended periods, may compromise the capillary integrity of the underlying tissue and produce irritation. The injection of excessive volumes of local anesthetics with vasoconstrictor under pressure into tightly attached tissue may produce localized tissue ischemia and ulceration. The taut tissue overlying the hard palate is the most frequent location of this complication. High-pressure injection techniques, such as the periodontal ligament and intraosseous injections, have been reported to produce irritation and even necrosis of the interdental papilla, with exposure of the underlying bone. Self-inflicted injuries, such as cheek, lip, and tongue biting, are common causes of mucosal irritation after local anesthesia in children and occasionally in adults.

Infection

Although it is an extremely rare complication of local anesthesia with the use of sterile, single-use needles and cartridges, infection may result from injection into or through an infected area; the use of the same cartridge or needle in more than one patient (a major breech in patient safety); and multiple uses of the same needle in the same patient. Preparing the injection site with an antiseptic agent before injection may reduce the amount of bacteria at the site, but it is inconclusive as to whether this action prevents infection from intraoral needle injections.

Needle Breakage

Needle breakage is a rare occurrence during intraoral injection. The advent of the single-use, disposable needles coupled with high-quality manufacturing techniques have minimized this problem. However, unexpected patient movement, excessive lateral force by the operator, manufacturing defects, intentional overbending of needles, and use of 30-gauge needles have all been implicated in needle breakage. Needles are most susceptible to breakage at the needle-hub
Inappropriate needle selection may also contribute to failure. A needle that is too long or too short, coupled with uncertainty about the required depth of penetration, could lead to failure or breakage. The selection of a thin needle for certain injections may result in deflection as it passes through mucosa, muscle, and soft tissue away from the intended path of insertion. For this reason, a 25-gauge needle is preferable to a 27- or 30-gauge needle for intraoral injections. Occasionally, patients may experience some subjective signs of anesthesia but may not be able to withstand instrumentation without pain. This may be caused in part by injection of an inadequate volume of anesthetic solution or not waiting long enough for the action of the local anesthetic to penetrate the neural sheath. Increasing the volume of injected solution often remedies this problem. Increasing volume may also be of benefit in patients with anatomic variations. Patients who continually respond to vibration and pressure sensations despite profound local anesthesia probably require sedation or general anesthesia for complete comfort.

Cross-innervation from the contralateral side especially in procedures in and around the midline or from other less common neural elements must always be considered. In the mandible, variant branches of the inferior alveolar nerve may leave the nerve before it enters the mandibular foramen. These branches are not blocked by the conventional inferior alveolar nerve block. A more superiorly oriented injection may be necessary for success in a case such as this. The mylohyoid nerve, which supplies sensory and motor function to the mylohyoid muscle and anterior belly of the digastric, may enter the mandible on the lingual side by a foramen in the bicuspid region. This occurs in about 10% of patients and may provide sensory innervation to the incisor teeth. Again, an apparently successful conventional inferior alveolar block does not affect this nerve, and a higher injection or lingual infiltration may be necessary.

Finally, when the previously mentioned causes for failed anesthesia have been ruled out, the possibility of alternative innervation should be considered. Variant nerves may exist that supply structures not usually associated with them. This can occur in patients with an extremely high palate and long alveolar process. The nasopalatine nerve may exchange fibers with the anterior superior alveolar nerve, and contribute to the innervation of the incisor teeth. The long buccal nerve, although a branch of the third division of the trigeminal nerve, may innervate the buccal soft tissue in the maxillary molar area.

Occasionally, the pharyngeal plexus of nerves, which normally supply the pharynx, may supply impacted mandibular third molars. Very rarely the cutaneous colli nerve, a branch of the cervical plexus, may enter the mandible on the inner surface of the lingual cortical plate and provide accessory innervation to the mandibular teeth.

Another possible cause for failed local anesthesia is the presence of tissue inflammation. Because inflammation increases tissue blood flow, the systemic absorption of local anesthetic solutions is usually increased. Inflammation may also modify the activity of peripheral nerves by lowering the response threshold, changing the protein structure of the nerve, or enhancing conduction. Most significantly, inflammation lowers the tissue pH and creates an acidic environment. Lowered tissue pH significantly reduces the ability of local anesthetic drugs to block nervous tissue, and may render them ineffective. Injecting through areas of active inflammation is to be avoided and blocks more proximal to the lesion are advised.

**UPDATES AND FUTURE TRENDS**

This section updates changes in current practices and looks at possible future local anesthetic modalities and research possibilities. It serves to illustrate that nothing in medicine and dentistry is ever static. Who could have imagined a few years ago that local anesthetic effects could be shortened or reversed, or that major toxic reactions could be treated successfully? There is hope that advances in basic research will translate into clinical practice.

**Reversal**

One of the effects of local anesthetics that may be at best annoying, and at worst injurious, is the prolonged duration of soft tissue anesthesia beyond the therapeutic need. Prolonged numbness may result in difficulty with eating, drinking, speaking, and inadvertent cheek, lip, and tongue biting. Prolonged numbness is also a major cause of anxiety.
and severe behavioral problems in pediatric and special needs patients. Dentists have tried to decrease the duration by using infiltration instead of nerve block injections whenever possible, by using local anesthetics without vasoconstrictors and alternative techniques, such as intraligamentary injections with limited success. Recently, phentolamine mesylate (OraVerse) has been introduced to reduce the duration of dental anesthetics. Phentolamine is a nonselective \( \alpha \)-adrenergic blocking agent that was initially used to treat hypertension. Clinically, when injected into the anesthetic site, it produces a localized vasodilation. It is postulated that the injection of phentolamine into an area awash with local anesthetic would result in an accelerated clearance of the local anesthetic from the submucosal tissue and thus shorten the duration of effect. Hersh and colleagues\(^17\) studied the effects of phentolamine on the duration of soft tissue anesthesia in adolescents and adults. There was an 85-minute reduction in the median time to recovery of normal lip sensation compared with control subjects. Tavares and colleagues\(^18\) studied the effects of phentolamine in pediatric patients aged 4 to 11 years. There was greater than a 55% reduction in the median time to return to normal lip sensation, and a 60% reduction in the median time to return of normal tongue sensation compared with control subjects. No cardiovascular or other side effects were evident in either adult or pediatric patient groups. Phentolamine was determined to be safe and well-tolerated in adults and children. Studies are currently underway to determine the safety and efficacy of phentolamine in children younger than the age of 4. Phentolamine is supplied in a cartridge that fits into a standard dental syringe. The drug is injected directly into the same area, in the same volume as the original local anesthetic solution.

**Lipid Emulsions and the Treatment of Toxicity**

Bupivacaine is known to cause rapid and resistant cardiac toxicity when administered rapidly in high concentrations and volumes. In 1998, Weinberg and colleagues\(^19\) demonstrated that the doses and serum concentrations of bupivacaine required for cardiac toxicity in rats were increased when the rats were pretreated with a lipid emulsion (Intralipid; Fresenius Kabi, Uppsala, Sweden). It is postulated that a “lipid sink” is created, which reduces the serum concentration by removing bupivacaine from the sites of action in the myocardium and reversing the bupivacaine-induced cardiac toxicity. There have been several case reports of the successful use of Intralipid to reverse the cardiac toxicity of local anesthetics.\(^{20,21}\) Treatment of local anesthetic toxicity with lipid emulsions has become so successful that it is now a part of the Advanced Cardiac Life Support Guidelines for the treatment of local anesthetic toxicity.\(^{22}\)

**Buffering**

Local anesthetics containing vasoconstrictors are acidic solutions, which when injected, dissociate into an uncharged base form and a cationic form. The uncharged base diffuses into the nerve where it dissociates again to occupy sodium channels. It has been theorized that buffering the anesthetic solution to raise its pH should increase the amount of base form available for diffusion into the nerve. This would result in a faster onset with better efficacy compared with standard vasoconstrictor-containing solutions. The carbonation of the anesthetic may also diminish pain on injection and increase the depth of anesthesia by concentrating the local anesthetic molecules by ion-trapping. Several authors have reported an increased rate of onset and intensity of peripheral nerve blocks with buffered local anesthetics.\(^{23,24}\) A recent study, however, failed to confirm a faster onset, greater success, or less pain with buffered versus standard lidocaine with epinephrine for inferior alveolar nerve block.\(^{25}\) Buffering of local anesthetic solutions in dentistry has always been hampered by the decrease in shelf-life of the solutions and the difficulty of buffering the drug in a dental cartridge. OnPharma, Inc. (Los Gatos, CA) has developed a mixing pen device that enables the dentist to remove a set volume of local anesthetic from a dental cartridge immediately before injection and replace it with the same volume of sodium bicarbonate. This technique makes buffering easier and more available, but more studies are needed to confirm its benefits for routine dental or surgical procedures.

**Mannitol**

In a further attempt to increase the efficacy of local anesthetics, the osmotic diuretic mannitol has been added to local anesthetic solutions to increase diffusion. Mannitol’s principle use is to reduce the risk of perioperative renal failure, help chemotherapeutic agents cross the blood-brain barrier, and treat cerebral edema. The perineural sheath surrounding the nerve trunk acts as a diffusional barrier for local anesthetics. This may lead to incomplete blockade, as is sometimes seen with blocks of the inferior alveolar nerve. The addition of this hyperosmolar solution can shrink the perineural sheath and allow the anesthetic to penetrate more readily.\(^{26}\) Mannitol has been shown to be effective in opening the perineural membrane.\(^{27}\)
Wolf and colleagues\textsuperscript{28} examined the effect of the addition of mannitol to lidocaine 2\% with 1:100,000 epinephrine compared with a mannitol-free solution for an inferior alveolar nerve block. They were able to demonstrate that the addition of mannitol significantly improved the effectiveness of the block. Although the results are promising, this technique is still in its experimental phase.

**Extended-release Bupivacaine**

Long-lasting postoperative pain control is an important issue after extensive oral surgical procedures. Traditional postoperative opioid prescriptions, although somewhat effective, have been associated with adverse effects, abuse, and over-prescribing. A multimodal approach to pain control improves postoperative pain outcomes. This approach combines different modalities targeting different pain mechanisms. For example, a patient may be given preoperative oral nonsteroidal anti-inflammatory agents, intravenous sedation, or general anesthesia in which opioids or ketamine are used; intraoral injection of long-acting local anesthetics; perioperative steroids; and intravenous ketorolac or acetaminophen. Recently, a new drug delivery system has been introduced that may have future application in oral surgery. Pacira Pharmaceuticals (Parsippany, NJ) has received Food and Drug Administration approval for a bupivacaine liposome injectable suspension marketed as Exparel. Bupivacaine is encapsulated in DepoFoam (Pacira Pharmaceuticals), an extended-release liposomal drug delivery technology. DepoFoam is a microscopic, spherical honey-combed structure with internal chambers filled with encapsulated bupivacaine. After injection, the drug is released over time as the particles erode. In a study evaluating this extended-release bupivacaine delivery system for pain control after hemorrhoidectomy, Gorfine and coworkers\textsuperscript{29} showed a 30\% reduction in pain 72 hours postoperatively compared with placebo. They also noted a reduction in the amount of rescue medication (morphine) needed for breakthrough pain. Extended-release bupivacaine offers exciting possibilities for the future of postoperative pain control in oral surgery.

**Intranasal Tetracaine**

It has been reported that there is a 33\% failure rate when anesthetizing the maxillary central incisor with the anterior superior alveolar block.\textsuperscript{30} When the nasopalatine nerve was blocked in addition, the success rate reached 100\%. A 2:1 relationship was demonstrated between the anterior superior alveolar nerve and the nasopalatine nerve for central incisor innervation. It is known that fibers of the superior alveolar plexus occasionally join the nasopalatine nerve just below the nasal floor and travel with the nasopalatine nerve to reach the central incisor.\textsuperscript{31} Physicians and oral surgeons have long applied topical local anesthetics to the nasal cavity. Noorily and coworkers\textsuperscript{32} compared the effects of cocaine, lidocaine, and tetracaine on nasal mucosa and determined that tetracaine produced superior long-lasting nasal anesthesia. Because tetracaine is hydrolyzed by pseudo-cholinesterase, toxic reactions, if any, would be brief. Because tetracaine is capable of producing profound nasal anesthesia it might also be effective in anesthetizing branches of the anterior superior alveolar and nasopalatine nerves. Currently, there is ongoing interest in evaluating the efficacy of an intranasal tetracaine spray to act as a functional dental anesthetic for maxillary anterior teeth.

**Ropivacaine**

Ropivacaine was approved for clinical use in 1996. Structurally related to mepivacaine and bupivacaine, it was found to have low toxicity, a long duration, and selectivity for nerve fibers responsible for pain transmission. Ropivacaine seems to have a 70\% to 75\% greater margin of safety than bupivacaine.\textsuperscript{33} Cardiac toxicity is reduced because it contains only the S-enantiomer, whereas bupivacaine is a racemic mixture. El-Sharrawy and Yagiela\textsuperscript{34} compared various concentrations of ropivacaine for use as an injectable local anesthetic for inferior alveolar nerve block. The 0.25\% and 0.375\% solutions had a slow onset and produced poor surgical conditions. The 0.5\% and 0.75\% concentrations had a rapid onset and produced good surgical conditions lasting more than 3 hours. Although the pKa values are equal, ropivacaine had a much faster onset than bupivacaine because of weaker binding to extraneural and submucosal tissues. This allows for more rapid diffusion to the site of action. The long duration is attributed to ropivacaine’s inherent vasoconstrictive properties. Further studies in dental models evaluated the efficacy of a plain 0.75\% solution of ropivacaine compared with one containing epinephrine.\textsuperscript{35} The addition of epinephrine did not improve the quality or duration of effect, so the addition of a vasoconstrictor is not necessary for the use of ropivacaine in dentistry. Additionally, ropivacaine has proved successful for third molar surgery and for maxillary infiltration anesthesia.\textsuperscript{36,37} At this time, the main disadvantage to the routine use of ropivacaine in dentistry is that it is not available in dental cartridges. Otherwise, it has advantages over bupivacaine in that it is more rapid-acting, does not require a vasoconstrictor, and produces less central nervous system and
cardiac toxicity. Ropivacaine would be a welcome addition to the dental local anesthetic armamentarium. Consideration should be given to its manufacture and availability for dentistry.38

New Local Anesthetic Formulations

The adverse effects of vasoconstrictors in patients with significant cardiovascular system impairments are a real issue whenever the risks or benefits of a particular local anesthetic are considered. Although plain solutions are valuable, readministration may be necessary to augment the duration and effect. Prilocaine and articaine are available in reduced vasoconstrictor concentrations (1:200,000 epinephrine), but there is some concern about an increased incidence of paresthesia with mandibular block anesthesia with these 4% solutions. The potential advantages of ropivacaine as a plain solution are clear, but cost and availability are factors. The efficacy of lidocaine with 1:200,000 epinephrine has been compared with lidocaine with 1:100,000 epinephrine, and no clinical difference was detected in success or failure between these two concentrations.39 Articaine 4% with 1:400,000 epinephrine was shown to be adequate for pain control and hemostasis during dental treatment, although decreasing its duration of action.40 With the combination of an aging population, increasing medical complexity, wide spectrum of drug interactions, and medical and surgical advances, the application of local anesthesia is not static, but dynamic. Newer drugs and techniques continue to impact the ability to treat patients safely and effectively.

SUMMARY

Local anesthesia remains the foundation of pain control in dentistry especially when combined with moderate-deep sedation for invasive and painful procedures in the contemporary oral and maxillofacial surgical model. Dentistry has never had the choice of local anesthetic drugs and techniques that can be tailored to individual patients and procedures as are available today. Local anesthetics remain the safest and most effective drugs in medicine and dentistry to relieve intraoperative and postoperative pain. It is only with a thorough understanding of pharmacology and anatomy that clinicians have the basic clinical foundation to enhance the care of patients.

REFERENCES

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