Advances in Local Anesthetics: pH Buffering and Dissolved CO₂

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LEARNING OBJECTIVES
After participating in this CE activity, the individual will learn:
• An overview of local anesthetic pharmacology.
• The benefits of ex vivo buffering of local anesthetic.

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Disclosure: Dr. Falkel is a co-founder and chief medical officer of Onpharma.

INTRODUCTION
Local anesthetics are the safest and most effective drugs in medicine for the prevention and management of pain. The first widely used dental anesthetic was cocaine, then procaine and lidocaine. All of these local anesthetic solutions have been formulated with vasoconstrictors, most often with epinephrine, but in some cases with levonordefrin. Other anesthetics with properties useful in specific circumstances have been used in dentistry as substitutes for lidocaine, such as bupivacaine (long duration of analgesia), mepivacaine (effective for a short duration without a vasoconstrictor), and prilocaine (effective without a vasoconstrictor). Articaine has been available in the United States since 2000 and generally has the same anesthetic characteristics as lidocaine.

Recent technical advances have made it practical to alkalinize dental anesthetic cartridges at chairside, immediately prior to injection. Alkalinization hastens the onset of analgesia and reduces injection pain, making the science of buffering local anesthetic worthy of consideration by dentists interested in anesthesia that is more rapid, more efficient, and more predictable, as well as being more comfortable for the patient.

This article provides an overview of local anesthetic pharmacology, with an emphasis on pH, dissociation constant (pKₐ), bicarbonate buffering, and the collateral benefits provided by the dissolved CO₂ that is created in the bolus of the injection as a result of the bicarbonate buffering process.

ANESTHETIC FORMULATIONS
The molecular structures of typical local anesthetics are shown in Figure 1. All local anesthetics are amphipathic; that is, they possess both lipophilic and hydrophilic characteristics,
generally at opposite ends of the molecule. The largest portion of the molecule is the lipophilic portion. At the other end of the molecule is the hydrophilic portion. The anesthetic structure is completed by an intermediate hydrocarbon chain containing either an ester or an amide linkage.

Local anesthetics are classified as either amino esters or amino amides by their intermediate chain. The nature of this intermediate linkage is important in defining several properties of the local anesthetic, including the basic mode of biotransformation. Ester-linked local anesthetics (Figure 1) such as procaine and tetracaine are readily hydrolyzed in aqueous solution. Amide-linked local anesthetics (Figure 1) such as lidocaine, articaine, mepivacaine, prilocaine, and bupivacaine are relatively resistant to hydrolysis and, as prepared in the laboratory, are poorly soluble in water. Amides are also unstable on exposure to air. Being weakly basic, these anesthetics readily combine with acids to form local anesthetic salts, in which form they are quite soluble in water and comparatively stable.

**THE pH OF COMMERCIAL LOCAL ANESTHETICS FOR DENTISTRY**

In compounding local anesthetics for dental injection, manufacturers first combine the local anesthetics with hydrochloric acid (HCl) to form their hydrochloride salts (eg, lidocaine HCl), and then these salts are dissolved in sterile water. These "plain" local anesthetic solutions typically have a pH of about 5.5.

However, vasopressors (such as epinephrine) are added to the most commonly used dental anesthetics in order to inhibit circulation in the area of the injection, thereby limiting systemic uptake, decreasing toxicity, reducing bleeding, and extending the duration of analgesia. Epinephrine oxidizes readily at more alkaline pH levels and accordingly, lidocaine with epinephrine in anesthetic cartridges has been commonly distributed with sufficient HCl to achieve a pH between 3.3 and 5.5, per the United States Pharmacopeia (USP) Compendia of Standards.\(^1\) This range is relatively acidic, and dental anesthetic buffering studies have measured cartridges toward the bottom of the range, at pH 3.5,\(^2\) as well as below the USP range at 2.92.\(^3\) As oxidation occurs in commercial anesthetic cartridges during storage, either at the manufacturer or on a shelf in a dental office, the cartridges become more acidic and presumably lose some of their epinephrine to degradation over time, primarily through oxidation.\(^4\)

Hondrum and Ezell\(^4\) studied the changes that occur in dental anesthetic cartridges after they are manufactured and found that, among 9 lots of cartridges of lidocaine with epinephrine they tested (all of which were before their expiration dates), one measured below the USP minimum at 2.86.\(^4\) The loss of epinephrine over time through oxidation may account for the observation by some practitioners that their anesthetics become less effective toward their expiration dates.

**DISSOCIATION OF LOCAL ANESTHETICS**

Local anesthetic salts (eg, lidocaine HCl) are dissolved in either sterile water or saline and are both water soluble and stable. In solution, these anesthetics exist simultaneously as uncharged or deionized (RN) molecules and charged or cationic (RNH\(^+\)) molecules. The deionized lipophilic base is sometimes called the *active form*\(^5\) of the anesthetic. The relative proportion of each ionic form in the solution varies with the pH of the solution or surrounding tissues.

In the presence of a high concentration of hydrogen ions (at a lower more acidic pH), the equilibrium shifts to the left and most of the anesthetic solution exists in the charged form:

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

As hydrogen ion (H\(^+\)) concentration decreases (at a higher or more alkaline pH), the equilibrium shifts right toward the active or free base form:

\[
\text{RNH} + \text{H}^+ \rightleftharpoons \text{RN} + \text{H}_2\text{O} 
\]

The relative proportion of ionic forms also depends on the pK\(_a\), or dissociation constant, of the specific local anesthetic. The pK\(_a\) is a measure of a molecule’s affinity for hydrogen ion.
When the pH of the solution has the same value as the pKₐ of the local anesthetic, exactly 50% of the drug exists in the RNH⁺ form and 50% in the RN form. The percentage of drug existing in either form can be determined from the Henderson-Hasselbalch equation. The room temperature pKₐ of lidocaine is 7.9, Articaine is 7.8, and mepivacaine is 7.6 (Table 1).

**LIPID SOLUBILITY AND DIFFUSION**

Lipid solubility of a local anesthetic appears to be related to its intrinsic potency. The active form (RN) of local anesthetic is 4,000 times more lipid soluble than the cationic form (RNH⁺). Higher lipid solubility permits the active RN form of anesthetic to penetrate tissues and the nerve membrane (which itself is 90% lipid) more easily, while the nerve membrane presents a barrier to the cationic RNH⁺ form.

**PHYSIOLOGY, ANATOMY, AND THE KINETICS OF LOCAL ANESTHETICS**

**The Diffusion Process**—After depositing the local anesthetic as close to the nerve as possible, solution will diffuse in all directions according to prevailing concentration gradients. A portion of the injected local anesthetic diffuses toward the nerve and may cross the axonal membrane. However, a significant portion of the injected drug also diffuses away from the nerve. The following reactions occur after deposition of anesthetic:

- Some of the drug is absorbed by nonneural tissues (eg, muscle and fat)
- Some is diluted by interstitial fluid
- Some is removed by capillaries and lymphatics from the injection site (uptake)
- Some reaches the nerve.

The sum total of the first 3 factors is to decrease the local anesthetic concentration outside the nerve; however, the concentration of local anesthetic within the nerve continues to rise over time as diffusion into the nerve progresses.

**The Impulse Blocking Process**—The function of a nerve is to carry messages from one part of the body to another. In dentistry, the key concern is to temporarily disable the transmission or propagation of pain impulses to the brain from the area of treatment. The pain messages the clinician wishes to block are carried by nerves in a complex electrochemical process that is itself worth separate study, but cannot be addressed in detail here. For the purposes of this discussion, the key understanding is that nerve impulses propagate along myelinated nerves by jumping from node of Ranvier to node of Ranvier (Figure 2). As anesthetic reaches the nerve, active RN molecules diffuse across the nerve sheath at the nodes of Ranvier and enter the axoplasm. Because the axoplasm is more acidic than the surrounding tissue, some of the RN molecules that cross the nerve membrane will obtain a charge (H⁺) in the axoplasm and will become RNH⁺ molecules, which are capable of binding to receptor cites in the sodium channels, inhibiting impulse propagation. The diffusion process continues until an equilibrium results between the intraneural and extraneural concentrations of anesthetic solution. If sufficient anesthetic enters the nerve, the impulses at a node of Ranvier may be completely blocked. Because the nerve impulses jump from node of Ranvier to node of Ranvier and because these impulses are capable of jumping more than one node, complete analgesia is said to require blockade of at least 3 nodes of Ranvier, or a minimum of 8 mm of the nerve.

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**Table 1. Dissociation Constants (pKₐ) Local Anesthetics Used in Dentistry**

<table>
<thead>
<tr>
<th>Local Anesthetic Agent</th>
<th>pKₐ</th>
<th>Percent Base Form (RN) at pH 7.4</th>
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<tbody>
<tr>
<td>Mepivacaine</td>
<td>7.6</td>
<td>39%</td>
</tr>
<tr>
<td>Articaine</td>
<td>7.8</td>
<td>28%</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.9</td>
<td>24%</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.9</td>
<td>24%</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>17%</td>
</tr>
</tbody>
</table>
INCREASES IN pH AND THE ACTIVE RN FORM OF LOCAL ANESTHETIC
As discussed in the dissociation section above, the pH of the anesthetic solution affects the relative amount of the active RN form of anesthetic available in the bolus of the injection. Because local anesthetic solutions exist in a dynamic equilibrium, some of the molecules will be in the active RN form and some of the molecules will be in the inactive RNH+ form. The ratio of RN and RNH+ molecules in a given volume of local anesthetic is dependent on the pH of the solution per the Henderson-Hasselbalch equation; at a typical pH of commercial lidocaine solutions containing epinephrine (3.5), there will be approximately one molecule of active RN anesthetic for every 25,000 molecules of the inactive cationic RNH+ form. At a physiologic pH of 7.4, the ratio of active anesthetic (RN) is vastly improved to approximately one molecule of active RN form for every 3 molecules of the cationic RNH+ form.

ONSET TIME AND THE pH OF LOCAL ANESTHETIC INJECTIONS
Onset time for a peripheral block is the period of time from deposition of the anesthetic solution to complete analgesia of the treatment area. The pH of the anesthetic solution determines the initial availability of the active RN form of the anesthetic in a given injection. Since the body’s mechanism for raising the pH of injected anesthetic depends upon the bicarbonate found in the tissues and fluids at the injection site, the rate at which buffering occurs after a traditional local anesthetic injection will be dependent upon the individual’s physiology, as well as the state of the tissues in the area of the injection. Notably, infected tissue may have a pH as low as 5.0,5,9 which may explain why infected teeth are sometimes reported to be more difficult or even impossible to numb.

OPTIMIZING ACTIVE ANESTHETIC BEFORE INJECTION: pH BUFFERING
In clinical situations, the pH of the anesthetic at the time of injection has been shown to be a strong determinant of anesthetic latency. Raising the pH of local anesthetic (also called “anesthetic buffering” or “alkalinization”) immediately prior to injection using a bicarbonate solution represents an alternative to relying on the body to accomplish the equivalent pH change after injection. The ex vivo process (outside the body) uses the same chemical mechanism and molecule (NaHCO3) as the body will use to buffer the anesthetic after the injection in vivo (inside the body), but the ex vivo process represents a way to accomplish the pH change instantaneously and more dependably.

Alkalization has been part of the local anesthetic literature for more than 100 years. The first clinical report of improved onset time by combining sodium bicarbonate solution with procaine with epinephrine was by Gros in 1910.10 The first anesthesia textbook reference to anesthetic buffering (adding sodium bicarbonate to procaine with epinephrine) was made by Gwathmey and Baskerville in 1914.11 Today, leading textbooks in medical anesthesia12-16 and local anesthesia for dentistry17 teach that alkalization is the most effective method for improving anesthetic onset time. Among anesthesiologists, local anesthetic buffering is considered a sufficiently fundamental skill that it is taught in preparation for the Anesthesiology Boards.18-22 Until recent advances in technology made it expedient to buffer dental
anesthetic cartridges at chairside, buffering local anesthetic in dentistry had not been considered practical.

To illustrate the impact that ex vivo buffering can have on latency, following are 2 examples of anesthetic diffusion into the axoplasm using lidocaine with epinephrine buffered to physiologic pH (Example A), and nonbuffered standard lidocaine with epihrene (Example B).

**EXAMPLE A (BUFFERED INJECTION)**

1. Presume the injection contains 100,000 molecules of lidocaine approximately at physiologic pH (7.4), and that the injection is made at or near the inferior alveolar nerve (IAN).

2. From the Henderson-Hasselbalch equation, we can calculate that 25% (25,000) molecules will be in the active RN lipid soluble form, and 75% (75,000 molecules) will be in the cationic RNH⁺ form. Theoretically, all 25,000 RN molecules could diffuse through the nerve sheath to reach the interior (axoplasm) of the neuron and block nerve conduction.

3. After the RN molecules cross the nerve sheath into the more acidic environment of the axoplasm, they readily take on a hydrogen ion (H⁺), becoming RNH⁺ molecules which are unable to diffuse back out across the nerve membrane. Thus, most of these 25,000 molecules are trapped in the axon, a process that is called “ion trapping.” As the following steps show, ion trapping is a process that helps anesthetic molecules accumulate in the axoplasm, and is a key to ultimately achieving an anesthetic concentration inside the axon sufficient to create and maintain a block.

4. Meanwhile, outside the neuron, during this first cycle, the equilibrium between RNH⁺ and RN molecules has been disrupted by the passage of the 25,000 active RN molecules into the neuron. The remaining 75,000 extracellular RNH⁺ molecules now re-equilibrate per the Henderson-Hasselbalch equation. The calculation to re-achieve the 75%:25% ratio dictated by the tissue’s pH of 7.4 is:

   \[ \text{RNH}^+ (57,000 \text{ molecules}) \rightleftharpoons \text{RN} (18,000 \text{ molecules}) + \text{H}^+ \]

5. The 18,000 newly created active RN molecules diffuse into the cell, and 57,000 remain outside the axon, where the re-equilibration process described in Step 3 eventually occurs again as follows:

   \[ \text{RNH}^+ (42,750 \text{ molecules}) \rightleftharpoons \text{RN} (14,250 \text{ molecules}) + \text{H}^+ \]

6. After the 14,250 newly created RN molecules enter the axon, a third re-equilibration cycle occurs among the 42,750 RNH⁺ molecules, as follows:

   \[ \text{RNH}^+ (32,062 \text{ molecules}) \rightleftharpoons \text{RN} (10,688 \text{ molecules}) + \text{H}^+ \]

7. To summarize, after 3 re-equilibration cycles, about 70,000 molecules of lidocaine are trapped in the axon. Theoretically, these cycles continue until all local anesthetic molecules diffuse into the axoplasm. Of course, in reality, not every anesthetic molecule reaches the interior of the neuron through diffusion. Some are not in contact with the membrane, and some of the extra-axonal RN and RNH⁺ molecules will be absorbed into local blood vessels and carried off before they can cross the nerve membrane (preventing this “uptake” is a key benefit of the vasoconstrictor). In any case, it is clear that given enough time, much of the injected anesthetic will eventually be converted to the active RN form and will enter the nerve axoplasm.

8. Ultimately, when 3 successive nodes of Ranvier are blocked, analgesia is achieved.

**EXAMPLE B (STANDARD INJECTION)**

1. Presume the injection of 100,000 molecules of lidocaine at commercial pH (3.5) at or near the IAN.

2. From the Henderson-Hasselbalch equation, we can calculate that 0.004% (400) molecules will be in the active RN lipid soluble form, and 99.996% (99,600 molecules) will be in the inactive RNH⁺ form. Theoretically, all 400 of the RN molecules could diffuse through the nerve sheath to reach the interior (axoplasm) of the neuron.

3. After 3 re-equilibration cycles, about 1,600 RN molecules have been ion trapped, compared to the 70,000 molecules that were ion trapped in the buffered anesthetic example. At this rate, in order to achieve the same 70,000 RN molecules in the axon, it would require approximately another 175 re-equilibration cycles.

4. However, even as these re-equilibration cycles are occurring, 2 other things are happening: (a) The body’s tissues and fluids are gradually raising the pH of the extracellular anesthetic molecules—a process that is dependent upon the patient’s physiology; and (b) The vasculature in the area of the injection is carrying some of the anesthetic away in the uptake process, which is dependent upon the patient’s anatomy.
5. At this point it becomes very difficult to estimate the rate of ion trapping, which like latency, varies widely from patient to patient. Eliminating this variability, and thereby increasing predictability, is one of the most attractive features of buffering anesthetic outside the body.

6. In the second example, sufficient anesthetic may be eventually created via re-equilibration and in vivo buffering such that a successful block is created. According to

<table>
<thead>
<tr>
<th><strong>Glossary of Key Dental Anesthetic Terms</strong></th>
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<tbody>
<tr>
<td><strong>Alkalization</strong></td>
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<tr>
<td><strong>Analgesia</strong></td>
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<td><strong>Anatomical Miss</strong></td>
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<td><strong>Anesthetics</strong></td>
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<td><strong>Anesthetize</strong></td>
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<td><strong>Anesthesia</strong></td>
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<td><strong>Anesthetic Block</strong></td>
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<td><strong>Anesthetic Success</strong></td>
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<td><strong>Anesthetic Failure</strong></td>
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<td><strong>Extra-Axonal</strong></td>
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<td><strong>EPT</strong></td>
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<tr>
<td><strong>IANB (or IAN Block)</strong></td>
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<tr>
<td><strong>Incomplete Anesthesia</strong></td>
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<td><strong>Infiltration Anesthesia</strong></td>
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<td><strong>Injection Pain (3 types)</strong></td>
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<td><strong>Lipsign</strong></td>
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<td><strong>Onset [of Analgesia]</strong></td>
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<tr>
<td><strong>Onset Time (also “Latency”)</strong></td>
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<td><strong>Pulpal Analgesia</strong></td>
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<td><strong>Regional Block</strong></td>
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<tr>
<td><strong>Soft-Tissue Analgesia</strong></td>
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<td><strong>Visual Analog Scale</strong></td>
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Fernandez and colleagues, for any one patient, this will take between 5 and 45 minutes and, if the practitioner waits the full 45 minutes, success will be achieved 95% of the time. These examples show that there is definitely room for improving the physiologic process of diffusion and buffering that must occur before an anesthetic injection creates analgesia. Many of the leading textbooks in local anesthesia recommend bicarbonate buffering to hasten onset of analgesia. In addition, 8 peer-reviewed published studies involving a total of 620 patients have evaluated the efficacy of buffering commercially prepared lidocaine with epinephrine in order to hasten the onset of analgesia, and all 8 concluded that buffering significantly improved latency. In December 2010, the Cochrane Collaboration published the results of its systematic review of buffering lidocaine solutions with sodium bicarbonate, concluding that ex vivo buffering is a safe and effective method for reducing local anesthetic injection pain.

**THE COLLATERAL BENEFITS OF BICARBONATEBUFFERING: CO₂**

The process of buffering a local anesthetic containing hydrochloric acid using bicarbonate creates salt, water, and free carbon dioxide as byproducts of the buffering reaction. Investigators have shown that creating dissolved CO₂ in the local anesthetic has benefits in addition to raising the pH of the solution before injection. Catchlove demonstrated that free CO₂ in lidocaine solution had an independent anesthetic effect, which was similar to the effect that lidocaine had on peripheral nerves. He suggested that where a solution contains both lidocaine and free CO₂, it is the CO₂ that may cause the more immediate form of analgesia, writing:

“Since CO₂ diffuses rapidly through the sheath and has an independent anesthetic effect, it probably reaches the axon before the local anesthetic, causing the earliest phase of the block.”

In addition to the independent anesthetic effect identified by Catchlove, Bokeh et al demonstrated that CO₂ served as a catalyst for the anesthetic process using lidocaine. Their study showed a significantly more profound conduction block when free CO₂ was present in lidocaine solution. Raymond and colleagues reported that lidocaine was twice as potent in the presence of free CO₂. Condouris and Shakalis reported that free CO₂ caused a tenfold increase in procaine action.

**SUMMARY**

The physiology, anatomy, and the kinetics of the time course of local anesthetics suggest that the body’s processes of converting the cationic RN⁺ form of local anesthetic to the active RN form are responsible for significant delay, uncertainty and inconsistency in anesthesia. Taking a patient’s physiology out of the latency equation by buffering the local anesthetic solution at chairside immediately prior to injection is an attractive alternative to waiting for the body to accomplish the same buffering process. Ex vivo bicarbonate buffering has been studied and written about for more than 100 years, it is a process recommended by the authors of the leading anesthesiology textbooks, and it is a process that has been evaluated in a recently published Systematic Review by the Cochrane Collaboration, which concluded that the sodium bicarbonate buffering of lidocaine is safe and effective for reducing injection pain.

Although it is clear that there are significant benefits to buffering the lidocaine solutions that represent the gold standard in dental anesthetics, the problem with adoption of this technique in dentistry (versus medical specialties such as emergency medicine where preinjection anesthetic buffering is common) has been that dental anesthetic cartridges are sealed containers that do not lend themselves to conveniently and precisely adding sodium bicarbonate solution prior to delivering the injection. The science of buffering and the need for more rapid and predictable onset (as well as for more comfortable injections) in dentistry has led to the development of a technology for buffering lidocaine with epinephrine at chairside using the Onset Mixing Pen with Sodium Bicarbonate Injection, 8.4% USP Neutralizing Additive Solution, both products by Onpharma (Figure 3).

**CLINICAL RECOMMENDATIONS FOR PRACTITIONERS**

*Buffer Cartridge Immediately Before Delivering the Injection—According to Catchlove,* Bokeh et al, Condouris and Shakalis, Ibusuki et al, and others as
referenced previously, the free CO$_2$ in solution that is created during the anesthetic buffering process plays a meaningful role in the improved performance of buffered local anesthetics. Delay in administering the buffered anesthetic can cause some of the CO$_2$ to come out of solution and adhere to the glass of the cartridge, reducing the benefits by eliminating the CO$_2$ from the bolus of the injection. Because of this, buffered anesthetic should be prepared chairside only when the clinician is ready to administer the injection. By no means should a practitioner or staff buffer cartridges in advance of procedures.

**Buffer Every Injection**—Practitioners should buffer each of their injections that include lidocaine with epinephrine. Whether the injection technique is an IANB, a palatal injection, an intraligamentary injection, a maxillary infiltration, a buccal infiltration, or another technique, raising the pH of the injection will increase the active anesthetic available immediately at the time of the injection and will eliminate the need for the body to buffer the anesthetic toward physiologic pH as part of the process of achieving analgesia. This will limit the uncertainty that is always inherent in any process that relies upon the patient’s unique physiology. It will also raise the pH of the injection toward physiologic, reducing the “bee sting effect” that some patients experience, even for those practitioners who generally deliver comfortable injections.

**Set Aside 15 to 20 Minutes at the Start of the First Day of Use to Train Staff on Buffering**—The cartridge buffering method and armamentarium described above can be used to buffer dental anesthetic cartridges in less than 5 seconds at chairside. However, dentists should spend time with staff that may either buffer the anesthetic cartridges or assist the dentist in buffering the anesthetic, so that each person involved can review and discuss the package insert for the neutralizing solution, review the instructions for use, and review the dentist’s aseptic technique. Key points of emphasis in the discussion are confirming the volume of buffering solution to use (per table in the package insert) and noting that buffering is only indicated for use with cartridges of lidocaine with epinephrine. Staff should practice buffering a few cartridges to get the feel for the process of connecting the anesthetic cartridge to the pen, dialing the pen, buffering the anesthetic cartridge, and then removing the anesthetic cartridge from the pen to be loaded into the dental syringe or other delivery device.

**Try Staying with the Patient**—The improved onset time allows practitioners to stay with the patient, as an improvement over the normal regime of leaving the patient after administering the injection, handling other tasks outside the operatory for a period of time, and then returning, regloving, and beginning the procedure. Formerly, the duration of the latency period made it impractical to stay with the patient until analgesia was achieved. Doctors who have used chairside buffering long enough to become familiar with its faster onset are finding it practical to remain with the patient and begin work without interrupting the process to leave the operatory. These practitioners have reported that by simply staying with the patient and completing the procedure without leaving, they are able to move the activities normally.
handled during the latency period (hygiene exams, checking e-mail, etc) to the back end of the appointment, and that they are ending up with a meaningful net gain in time, which is intuitive, considering the disruption in workflow inherent in leaving/returning to the operatory. They also report that their normal “interim tasks” are less hurried and/or stressful when a patient is not waiting for their return in the operatory chair. These are anecdotal reports, of course, but they may be helpful for practitioners who are wondering what practical experiences they may have if they evaluate buffering in their practices. Notably, practitioners report that patients are commenting on the difference it makes in their perception of the care they are receiving when their dentists stay with them in the operatory after delivering their injection.

**CONCLUSION**

Considering the central role that local anesthesia plays in a typical dental office, reducing latency and variability in the local anesthesia regime can improve patient care and reduce stress on the practitioner. Buffering local anesthetic can be an important tool for practitioners looking to improve their local anesthesia regime.

**REFERENCES**


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POST EXAMINATION QUESTIONS

1. Local anesthetics are classified as:
   a. Amino esters.
   b. Amino amides.
   c. Hydrochloride salts.
   d. Both a and b.

2. Procaine and tetracaine are readily hydrolyzed in aqueous solution. Lidocaine and articaine are poorly soluble in water.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

3. The active form of a local anesthetic is known as:
   a. RN.
   b. RNH⁺.
   c. HR.
   d. HR⁺.

4. The dissociation constant of a specific local anesthetic is known as its:
   a. KPA.
   c. pKₐ.
   d. pK.

5. The active form of local anesthetic is ______ times more lipid soluble than the cationic form.
   a. 1,000.
   b. 2,000.
   c. 3,000.
   d. 4,000.

6. The USP standards for the pH of cartridges of lidcaine with epinephrine is from 3.3 to 5.5. Studies measuring the pH change that occurs via oxidation during the shelf life of cartridges measured the pH as low as:
   a. 3.15.
   b. 3.00.
   c. 2.86.
   d. 1.86.

7. According to the Henderson-Hasselbalch equation, at a pH of 3.5 the ratio of ionized anesthetic molecules to active de-ionized anesthetic molecules is:
   a. 25:1.
   b. 15:1.
   c. 8,000:1.
   d. 25,000:1.
8. The following reaction occurs after deposition of local anesthetic:
   a. Some of the drug is diluted by interstitial fluid.
   b. Some of the drug absorbed by muscle and fat.
   c. Some of the drug is removed from the injection site by capillaries.
   d. All of the above.

9. Complete analgesia is said to require blockade of:
   a. One node of Ranvier.
   b. Two nodes of Ranvier.
   c. Three nodes of Ranvier.
   d. Four nodes of Ranvier.

10. Infected tissues may have a pH as low as:
    a. 2.5.
    b. 3.5.
    c. 4.0.
    d. 5.0.

11. In December 2010, the Cochrane Collaboration concluded that:
    a. In vivo buffering of lidocaine solutions is the only effective method for reducing local anesthetic injection pain.
    b. Ex vivo buffering of lidocaine solutions is a safe and effective method for reducing local anesthetic injection pain.
    c. Ex vivo buffering of lidocaine solutions has no apparent effect on local anesthetic injection pain.
    d. None of the above.

12. Both the in vivo and the ex vivo pH buffering of local anesthetic solution are accomplished using:
    a. Hydrochloric acid.
    b. Sodium bicarbonate.
    c. Magnesium phosphate.
    d. Carbon dioxide.

13. A byproduct of ex vivo buffering of local anesthetics containing hydrochloric acid that plays a meaningful role in the improved performance of the anesthetic is:
    a. Salt.
    b. Water.
    c. CO$_2$.
    d. All of the above.

14. Buffered lidocaine with epinephrine should be prepared chairside:
    a. One hour prior to injection.
    b. Up to 4 hours prior to injection.
    c. Up to 8 hours prior to injection.
    d. Only when the clinician is ready to administer the injection.

15. The injection technique that can be improved by chairside buffering of lidocaine with epinephrine solution is:
    a. Inferior alveolar nerve block.
    b. Palatal injection.
    c. Intraligamentary injection.
    d. All of the above.

16. Benefits of chairside buffering of lidocaine with epinephrine solution include:
    a. Reducing the “bee sting effect.”
    b. Inducing more rapid onset of analgesia.
    c. Eliminating the need for the body to buffer the anesthetic.
    d. All of the above.
PROGRAM COMPLETION INFORMATION

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Please check the correct box for each question below.

1. ☐ a ☐ b ☐ c ☐ d  9. ☐ a ☐ b ☐ c ☐ d
2. ☐ a ☐ b ☐ c ☐ d  10. ☐ a ☐ b ☐ c ☐ d
3. ☐ a ☐ b ☐ c ☐ d  11. ☐ a ☐ b ☐ c ☐ d
4. ☐ a ☐ b ☐ c ☐ d  12. ☐ a ☐ b ☐ c ☐ d
5. ☐ a ☐ b ☐ c ☐ d  13. ☐ a ☐ b ☐ c ☐ d
6. ☐ a ☐ b ☐ c ☐ d  14. ☐ a ☐ b ☐ c ☐ d
7. ☐ a ☐ b ☐ c ☐ d  15. ☐ a ☐ b ☐ c ☐ d
8. ☐ a ☐ b ☐ c ☐ d  16. ☐ a ☐ b ☐ c ☐ d

PROGRAM EVALUATION FORM

Please complete the following activity evaluation questions.

Rating Scale: Excellent = 5 and Poor = 0

Course objectives were achieved. __________________________

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Review questions were clear and relevant to the editorial. __________________________

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How much time did you spend reading the activity and completing the test? __________________________