Anesthetic Buffering: New Advances for Use in Dentistry

A Peer-Reviewed Publication
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Abstract
Local anesthetics are the safest drugs used in dentistry for pain management, but cause undesirable qualities such as stinging and burning upon injection, relatively slow onset of action, and unreliable or no anesthesia when injected into infected tissues. Buffering of local anesthetics has been demonstrated to counteract these undesirable qualities of local anesthetics. Recent advances in technology have made buffering of local anesthetics practical for use to alkalinize dental local anesthetic cartridges chairside immediately prior to injection, making the anesthetic's onset quicker, more reliable, and more comfortable for the patient. This article provides an overview of neurophysiology, pharmacology of local anesthetics, and the role and benefits of local anesthetic buffering.

Educational Objectives
The overall goal of this course is to familiarize the dental hygienist with current dental anesthetics. Upon completion of this course, the clinician will be able to do the following:
1. Overview of neurophysiology
2. Overview of local anesthetic pharmacology: structure of local anesthetics, properties and ionization factors of local anesthetics, dissociation constant (pK_a) and its effects on the onset of action of local anesthetics
3. Discuss the benefits of ex vivo buffering process

Author Profile
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Author Disclosure
Demetra Daskalos has no potential conflicts of interest to disclose.
Educational objectives
The overall goal of this course is to familiarize the dental hygienist with current principles of dental anesthetics. Upon completion of this course, the clinician will learn about:
1. Overview of neurophysiology
2. Overview of local anesthetic pharmacology: structure of local anesthetics, properties and ionization factors of local anesthetics, dissociation constant (pKₐ) and its effects on the onset of action of local anesthetics, infection, and decreased efficiency of local anesthetics
3. Discuss the benefits of ex vivo buffering process

Abstract
Local anesthetics are the safest drugs used in dentistry for pain management, but cause undesirable qualities such as stinging and burning upon injection, relatively slow onset of action, and unreliable or no anesthesia when injected into infected tissues. Buffering of local anesthetics has been demonstrated to counteract these undesirable qualities of local anesthetics. Recent advances in technology have made buffering of local anesthetics practical for use to alkalinate dental local anesthetic cartridges chairside immediately prior to injection, making the anesthetic’s onset quicker, more reliable, and more comfortable for the patient. This article provides an overview of neurophysiology, pharmacology of local anesthetics, and the role and benefits of local anesthetic buffering.

Introduction
Local anesthetics are agents that block the sensation of pain by reversibly blocking nerve conduction when applied to a circumscribed area of the body.¹ Local anesthetics have evolved into the safest drugs used in medicine for pain management and they are the most commonly used drugs in dentistry. However, there are several drawbacks associated with the administration of local anesthetics. Local anesthetics are acidic upon injection and cause stinging and burning, they are unreliable in areas of inflammation and infection, they have a relatively slow onset of action, and they can cause post-injection tissue trauma.² The most common complaint by patients in dentistry is the burning and stinging of injections due to the acidic anesthetic. The science of buffering of local anesthetics with vasoconstrictors has been researched to address all of these issues. It has been used in medicine for many years and has recently been introduced for use in dentistry.³⁻⁴ Anesthetic buffering eliminates the sting, reduces tissue trauma, and reduces the latency of local anesthetics.³⁻⁴

Neurophysiology
Local anesthetics interrupt neural conduction by interfering with the propagation of peripheral nerve impulses, thus inhibiting the influx of sodium ions during depolarization. In most cases, this follows the anesthetic’s diffusion through the neural membrane into the axoplasm, where it enters sodium channels and prevents an active or “open” state. Local anesthetics bind to specific recep-
it predetermines the course of biotransformation. Ester local anesthetics are hydrolyzed by appropriate esterases, and amide local anesthetics generally require enzymatic breakdown by the liver.

The hydrophilic terminal amine (or acid form) may exist in a tertiary form (three bonds) that is uncharged and lipid soluble or as a quaternary form (four bonds) that is positively charged and renders the molecule water soluble, which is how it is delivered from the dental hygienist’s syringe into the patient’s tissue.

![Figure 2: Local anesthetic action.](image)

A local anesthetic existing in equilibrium as a quaternary salt (RNH+) and tertiary base (RN) is essential for penetration of both the epineurium and neuronal membrane. Once the molecule reaches the axoplasm of the neuron, the amine gains a hydrogen ion, and this ionized quaternary form (RNH+) is responsible for the actual blockade of the sodium channel. Presumably, it binds within the sodium channel near the inner surface of the neuronal membrane. (From: Logothetis DD: Local anesthesia for the dental hygienist. St. Louis: Elsevier, 2012)

(Figure 2) As explained earlier, the aromatic ring determines the actual degree of lipid solubility, but the terminal amine acts as an “on-off” switch allowing the local anesthetic to exist in either lipid-soluble or water-soluble configurations. Once the anesthetic is injected into the tissue, the body buffers the local anesthetic toward the physiologic pH and dissociates the quaternary amine into uncharged tertiary amine base and a hydrogen ion which allows the anesthetic to penetrate the lipid-rich nerve membrane. Over time, as this in vivo buffering process continues, more and more of the un-ionized form of the anesthetic is available to penetrate the nerve, which ultimately leads to nerve blockade.

The tertiary amine following penetration of the nerve will once again gain a hydrogen ion in the axoplasm to successfully bind to the receptor sites. The tertiary and quaternary forms exhibit vital roles in the sequence of events leading to the conduction block, and the body’s buffering plays an integral role in this process.

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**Chemistry and pH of local anesthetics**

Synthetic local anesthetics are prepared as weak bases, and during manufacturing precipitate as powdered unstable solids that are poorly soluble in water. They are combined with an acid to form a salt (hydrochloride salt) to render them water soluble; these can be dissolved in sterile water or saline, creating a stable, injectable anesthetic solution.

The molecules exist in a quaternary water-soluble state in the cartridge, and are acidic. In the cartridge, the solution contains an equilibrium of positively charged (ionized) molecules, the acid or cation (RNH+), and uncharged (un-ionized) molecules, the base or anion (RN). The formula RNH+ (reverse-react) RN + H+ represents the equilibrium between the two ions and H+ as the hydrogen ion (Figure 3). The equilibrium is dependent upon the pH of the solution and the pKₐ (how easily the compound becomes charged).

When the pKₐ equals the pH, there is an equal distribution of charged cations and uncharged base molecules. If there is a high presence of H+ ions, the equilibrium shifts to the left and the anesthetic solution will have higher concentrations of the ionized (charged) cationic form, which is water-soluble and is the active form of the molecule (RNH+ > RN + H+). In contrast, if the presence of H+ ions is decreased, the equilibrium shifts to the right and the anesthetic solution will have a higher concentration of un-ionized (uncharged) free base which is fat soluble and is the form that penetrates the nerve membrane (RNH+ < RN + H+).

The pH (the acid-base balance) of the solution is manipulated by the manufacturer to complement the specific molecular structure of each anesthetic. However, all local anesthetic solutions are acidic before injection. The lower the pH, the more acidic the solution, and the higher the pH, the more alkaline (basic) the solution. Local anesthetic solutions without vasoconstrictors range in pH from approximately 5 to more than 6; generally, preparations with vasoconstrictors are more acidic than plain formulations because of the presence of the preservative (antioxidant) sodium bisulfite, and the pH ranges from approximately 3.3 to 5.5.

Once injected, the hydrophilic (ionized) component, which is
acidic, facilitates diffusion through the extracellular fluid to the nerve. However, the cation form will not penetrate the nerve. Therefore the time of onset of the local anesthetic is based on the proportion of the molecule that converts to the tertiary, lipid-soluble base structure when exposed to the normal physiologic pH (7.4) of the body. Once injected into the tissues (pH 7.4), the amount of local anesthetic in the free-base un-ionized form will increase to provide greater lipid penetration of the nerve. The increase in the base molecules is due to the dissociation of the H⁺ ion from the quaternary molecule, now rendering it a tertiary base molecule that can penetrate the nerve.¹,¹⁰ The dissociation constant (pKₐ) for the anesthetic predicts the proportion of molecules that exist in each of these states. By definition, the pKₐ of a molecule represents the pH at which 50% of the molecules exist in the lipid-soluble tertiary anionic (uncharged base) form and 50% in the quaternary water-soluble cationic (charged acid) form.² As the pH of the tissues differs from the pKₐ of the specific drug, more of the drug exists either in its charged or uncharged form. This is expressed in the Henderson-Hasselbalch equation: pKₐ – pH = log [RH⁺]/[R⁻] where [R⁻] is the concentration of un-ionized (uncharged) drug and [RH⁺] the concentration of ionized (charged) drug. This is important because the molecular form of the anesthetic that allows diffusion through the lipid-rich nerve membrane is the free base (RNH₂) portion of the molecule. Once the free base of the molecule reaches the axoplasm inside the nerve membrane, the amine gains a hydrogen ion and reverts back to the ionized quaternary (cationic) form (RNH⁺), the active form of the molecule that binds to the receptor site preventing the influx of sodium. Because the pH of the body tissue is 7.4, the ideal pKₐ of an anesthetic should be 7.4, indicating that 50% of the molecules are uncharged base, and quick diffusion through the lipid membrane would occur. However, the pKₐ of all local anesthetics have values greater than 7.5 except topical benzocaine, which is 3.5, and have a pH of approximately 5 to 6 in plain solutions and lower with vasoconstrictors; therefore a greater proportion of the molecules exist in the quaternary water-soluble form when injected into tissue having normal pH of 7.4.³ This causes the stinging associated with the anesthetic’s pH. The higher the pKₐ of the anesthetic, the lower the concentration of uncharged base molecules. This causes slower diffusion into the nerve cell and a slower onset of action of the local anesthetic. So, the proportion of cations and base molecules is determined by the pH of the anesthetic, pKₐ of the anesthetic, and the pH of the tissue.¹,²,¹⁰

Infection in the area of injection
Tissue acidity — a result of many dental diseases — can impede the development of local anesthesia. The normal pH of the tissue is 7.4, and the solution in the cartridges predominately cationic (acidic). When the solution is injected into the tissue, the alkalinity of the tissue liberates the free base, allowing penetration of the local anesthetic molecule into the lipid-rich nerve. The acidic environment associated with an active infection causes a much lower tissue pH in the vicinity of 5-6, which favors the quaternary water-soluble configuration and the amount of free base is reduced even further, leaving fewer base molecules to penetrate the nerve. This is one reason why it is difficult to achieve dental anesthesia when infection is present. Other factors for failure of anesthesia are edema and the increase in inflammation associated with infections. The selection of an anesthetic with a lower pKₐ such as mepivacaine (pKₐ 7.7), would most likely provide more effective anesthesia than bupivacaine (pKₐ 8.1).¹,¹²

The role of anesthetic buffering to create a more comfortable and effective injection
As previously discussed, chemically, amide local anesthetics are weak bases. They are combined with an acid to form a salt (hydrochloride salt) to render them water soluble, creating a stable, injectable anesthetic solution. Therefore, all local anesthetic solutions are acidic before injection, ranging in pH from approximately 5 to 6 in preparations without a vasoconstrictor, and 3.3-5.5 in preparations with vasoconstrictors. Due to the acidic nature of the local anesthetic, there are several disadvantages such as: stinging or burning sensation on injection, which represents one of the most common complaints from patients, post-injection tissue injury, and unreliability of local anesthetic action in the presence of infection and inflammation.² The pH of the solution is important because it affects the way anesthetic works. The un-ionized (base) form that is lipophilic readily penetrates the nerve membrane to enter the nerve axon, where the anesthetic attaches to receptors on the sodium channels, resulting in a blockade of nerve conduction. After injection, tissue buffering raises the pH and a percentage of the drug dissociates to become free bases, the amount depending upon the dissociation constant of the individual anesthetic, allowing the free base to penetrate the lipid cell membrane to reach the interior of the axon where a portion of the anesthetic re-ionsizes. The re-ionized portion enters and plugs the sodium channels so that sodium ions cannot depolarize. As a result, action potentials are neither generated nor propagated and conduction block occurs.² The onset time for a peripheral block is the period of time from deposition of the anesthetic solution near the nerve trunk to complete analgesia of the treatment area. This is dependent upon the pH of the anesthetic solution, and the patient’s physiological mechanism for raising the pH, which is dependent upon the amount of bicarbonate in the tissue and fluid at the injection site, and the state of the tissues in the area of the injection. This is particularly of concern if infection is in the area of the injection, and explains why the infected tissues are difficult or impossible to numb.¹,²

Alkalization has been reported in local anesthetic literature for more than 100 years, and anesthetic buffering has been widely accepted in medicine as a way to make local anesthetic injections more comfortable, particularly in ophthalmology,¹¹ ear, nose and throat,¹² and dermatology.¹³ Because prefilled cartridges of local anesthetics are not used in medicine, it is relatively simple for the physician to add a volume of NaHCO to the local anesthetic
prior to injection. In dentistry, due to the prefilled, manufactured local anesthetic cartridge, it was difficult for the practitioner to buffer anesthetics prior to injection. A recently introduced product (February 2011) for use in dentistry by Onpharma® using a mixing pen and cartridge connectors provides an automated way to adjust the pH of lidocaine with epinephrine cartridges at chairside immediately prior to injection. (Figures 3 and 4) This provides the practitioner a way to neutralize the anesthetic by raising the pH of the local anesthetic immediately before the injection ex vivo (outside the body) rather than the in vivo buffering process, which relies on the patient’s physiology to buffer the anesthetic. Some authors suggest that bringing the pH of the anesthetic toward physiologic before injection may improve patient comfort by eliminating the sting, may reduce tissue injury, may reduce anesthetic latency, and may provide more effective anesthesia in the area of infection.4,7,13,14 For example, buffering lidocaine with epinephrine raises the pH from 3.3 to 7.4 and produces a 6,000 fold increase in active ionized anesthetic.14 Other authors were unable to demonstrate any improvement.15-17

The buffering process uses a sodium bicarbonate solution that is mixed with the cartridge of local anesthetic such as lidocaine with epinephrine. The interaction between the sodium bicarbonate (NaHCO3) and the hydrochloric acid (HCL) in the local anesthetic creates water (H2O) and carbon dioxide (CO2).15 The CO2 diffuses out of solution immediately and continues after the solution has been injected.19 Catchlove concluded that the CO2 in combination with lidocaine potentiates the action of lidocaine by a direct depressant effect of CO2 on the axon, concentrating the local anesthetic inside the nerve trunk through ion trapping, thus changing the charge of the local anesthetic inside the nerve axon.19 Catchlove18 and other researchers19,20 have demonstrated that CO2 has independent anesthetic effects which enhance the anesthetic’s action sevenfold.

Clinical recommendations for practitioners include buffering cartridges immediately before anesthetic delivery as previously discussed to enhance the performance of lidocaine with epinephrine and to reduce the anesthetic's discomfort. Delay in administering the buffered solution will result in some of the CO2 to adhering to the glass of the cartridge, reducing its benefits. Therefore, the buffering procedure should be completed chairside by the clinician at the time the injection is to be administered. Prior to use, the onset mixing pen is used as a compounding and dispensing device to mix the two solutions together. Once assembled, the pen enables the precise transfer of fluid of sodium bicarbonate from a standard 3 mL size cartridge into the 1.8 mL anesthetic cartridge, allowing the two solutions to be mixed. (Figure 4)

Figure 4:

Assembled mixing pen is a compounding and dispensing device used to mix two solutions together. Once assembled, the pen enables the precise transfer of sodium bicarbonate from a standard 3 mL size cartridge into the 1.8 mL anesthetic cartridge, allowing the two solutions to be mixed. Photo courtesy of Onpharma Inc., Los Gatos, CA

Figure 5:

The cartridge connector is used for the transfer of sterile solutions from one sealed container into a second sealed container and provides a reservoir for collecting excess solution displaced from the second sealed container during the transfer process. Photo courtesy of Onpharma Inc., Los Gatos, CA

The cartridge connector is used for the transfer of sterile solutions from one sealed container into a second sealed container and provides a reservoir for collecting excess solution displaced from the second sealed container during the transfer process. (Figure 5) Practitioners may use this buffering process on all injections utilizing lidocaine with epinephrine, whether administering a block, infiltration, intraligamentary injection, or other local anesthetic techniques. A more rapid onset of action will allow the clinician to begin treatment quicker, and will provide the patient with a more comfortable experience.

Conclusion
The induction of local anesthesia is dependent upon the patient’s physiologic process of converting the cationic RNH+ to the anionic RN form, and back to the RNH+ active form. This dissociation process is dependent upon the patient’s tissue pH and the pH of the administered drug, and can be responsible for a delayed onset of action, and overall inconsistency of anesthesia. Buffering of local anesthetics prior to injection takes the physiology out of the process, and provides an alternative to the in vivo process.
This alternative allows the process to be completed by the clinician ex vivo, and provides the benefit of a quicker onset of action, enhanced independent anesthetic effects, and an overall more comfortable injection for the patient. The recent introduction of the NaHCO and delivery devices developed to accommodate the dental anesthetic cartridges has offered the dental profession an easy way to accomplish chairside anesthetic buffering. As with any new product, more research is needed to determine the advantages, disadvantages, and consistency of results.

References

Author profile
Demetra Daskalos Logothetis RDH, MS is Professor Emeritus at the University of New Mexico Department of Dental Medicine, and currently Visiting Professor, and Graduate Program Director, Division of Dental Hygiene. Demetra has been a Professor at the University of New Mexico for 26 years, and served as the Dental Hygiene Program Director for 16 years. She has been teaching local anesthesia for 17 years, and is the author of Local Anesthesia for the Dental Hygienist, a new textbook by Elsevier Publishing (copyright 2012) exclusively related to local anesthesia for the practice of dental hygiene.

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Questions

1. Preinjection buffering to neutralize the local anesthetic prior to injection can provide which of the following advantages?
   a. Improved hemostasis
   b. Improved efficacy in areas of infection
   c. Increased duration of action of the local anesthetic
   d. Increase in protein binding of anesthetic

2. Infection and inflammation cause the following effect when administering a local anesthetic.
   a. Makes the local anesthetic more effective
   b. Inhibits the dissociation of the local anesthetic molecule
   c. Increases the duration of action of the local anesthetic
   d. Causes the inflamed tissue to have a high pH

3. Which part of the chemical structure of a local anesthetic determines if the local anesthetic agent is classified as an ester or an amide?
   a. Intermediate chain
   b. Aromatic ring
   c. Terminal amine
   d. Quaternary amine

4. Local anesthetics work by:
   a. Penetrating the nerve to inhibit Cl⁻ influx
   b. Penetrating the nerve to inhibit Na⁺ influx
   c. Penetrating the nerve to inhibit K⁺ efflux
   d. Penetrating the nerve to inhibit Na⁺ efflux

5. The quaternary form of the local anesthetic molecule:
   a. Is the ionized form in the cartridge and is responsible for binding to the receptor site
   b. Is the un-ionized form in the cartridge and is responsible for binding to the receptor site
   c. Is the ionized form of the molecule that penetrates the nerve membrane
   d. Is the un-ionized form of the molecule that penetrates the nerve membrane

6. Local anesthetics are dispensed by the manufacturer in local anesthetic cartridges as:
   a. Ionized bases
   b. Ionized acid
   c. Un-ionized base
   d. Un-ionized acid

7. Local anesthetic buffering has been difficult to achieve in the past due to:
   a. Prefilled manufactured local anesthetic cartridges
   b. Clinical time needed to perform the buffering
   c. Patient resistance
   d. Tissue resistance to buffering agents

8. Anesthetic buffering of local anesthetic solution is accomplished by using:
   a. Hydrochloric acid
   b. Carbon dioxide
   c. Sodium bicarbonate
   d. pKₐ enhancers

9. The pH of local anesthetics with vasoconstrictors are as low as:
   a. 3.3
   b. 4.8
   c. 5.5
   d. 6.0

10. Buffering of local anesthetic solutions should be prepared:
    a. Half hour before the injection
    b. One hour before the injection
    c. Immediately before the injection
    d. Up to 2 hours before the injection
Anesthetic Buffering: New Advances for use in Dentistry

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COURSE OBJECTIVES

1. Overview of neurophysiology
2. Overview of local anesthetic pharmacology: structure of local anesthetics, properties and ionization factors of local anesthetics, dissociation constant (pKa) and its effects on the onset of action of local anesthetics.
3. Discuss the benefits of ex vivo buffering process

Course Evaluation

1. Were the individual course objectives met? Objective #1: Yes No

2. To what extent were the course objectives accomplished overall? 5 4 3 2 1

3. Please rate your personal mastery of the course objectives. 5 4 3 2 1

4. How would you rate the objectives and educational methods? 5 4 3 2 1

5. How do you rate the author’s grasp of the topic? 5 4 3 2 1

6. Please rate the instructor’s effectiveness. 5 4 3 2 1

7. Was the overall administration of the course effective? 5 4 3 2 1

8. Please rate the usefulness and clinical applicability of this course. 5 4 3 2 1

9. Please rate the usefulness of the supplemental weblogly. 5 4 3 2 1

10. Do you feel that the references were adequate? Yes No

11. Would you participate in a similar program on a different topic? Yes No

12. If any of the continuing education questions were unclear or ambiguous, please list them.

13. Was there any subject matter you found confusing? Please describe.

14. How long did it take you to complete this course?

15. What additional continuing dental education topics would you like to see?

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