Local Anesthetics in Dentistry

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Faculty Disclosure

Contributing faculty, Mark J. Szarejko, DDS, FAGD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Director Disclosure

The director has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all dental professionals whose patients may be administered local anesthetics.

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Course Objective

The purpose of this course is to provide dental professionals with a comparative perspective on the use of local anesthetics.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the history of local anesthetics.
2. Compare and contrast ester-type and amide-type local anesthetics.
3. Describe the basic neurophysiologic mechanisms of action of local anesthetics.
4. List the most common local anesthetics used in dentistry today, including pharmacologic properties and contraindications.
5. Discuss the available topical anesthetics used in conjunction with local anesthetics in dentistry.
6. Analyze the action of buffering solutions and anesthetic reversal agents.

INTRODUCTION

Every day, dental patients undergo a variety of painless procedures, largely due to the efficacy of modern local anesthetics. "Painless dentistry" with the use of local anesthetics has become such a normal expectation that these medications are often taken for granted.

This course will begin with the history of local anesthetics, including the development of the predecessors of today's agents and their chemical classification. The physiology of neural conduction and the process by which local anesthetics interrupt this process to induce a temporary loss of sensation will be discussed, as it is critical to the understanding of how local anesthetics act. The most frequently used agents will be explored, including indications and contraindications of use and pharmacologic properties. Other components in anesthetic solutions, such as vasoconstrictors and preservatives, will also be discussed. The development and use of buffering solutions and anesthetic reversal agents will be reviewed, with a focus on their role facilitating the diminution of local anesthesia.

Although local anesthetics are largely safe, clinicians should not become complacent about their use, as medical emergencies are possible following their use. Clinicians should use their best judgement in selecting a local anesthetic based on the patient's medical history and the planned dental procedure(s).

AN HISTORICAL PERSPECTIVE

The use of modern local anesthetics was preceded by centuries of attempts to control acute and chronic odontogenic pain and to prevent pain during dental procedures. While these early methods are primitive by today's standards, their continual refinement and progression has led to a modern armamentarium of options to control and prevent pain related to dental procedures effectively and safely.

Today, cocaine is recognized as a harmful illicit drug, but it was also the predecessor of the current group of local anesthetics used in dentistry. Cocaine is derived from the coca plant (*Erythroxylum coca* or *Erythroxylum novogranatense*) native to western South America [1]. Indigenous groups would chew the leaves of the coca plant to elevate mood, aid digestion, and suppress the appetite [2]. In 1859, the chief alkaloid of coca was isolated and named "cocaine."

Cocaine is one of the only naturally occurring local anesthetics, along with neurotoxins (e.g., tetrodotoxin), menthol (derived from mint), and eugenol (derived from certain essential oils, such as clove). All modern local anesthetics are synthetic in origin. In 1884, Dr. Karl Koller introduced the use of cocaine for analgesic purposes in the field of ophthalmology [3]. The same year, Dr. William Halstead (a physician) used an injection of cocaine to successfully anesthetize the inferior alveolar nerve for the painless extraction of a patient's mandibular tooth [4]. Advertisements for over-the-counter cocaine drops that promised an instantaneous cure from toothache pain were promoted as early as 1885 [5].

The initial use of cocaine for medical purposes was done without knowledge of its adverse effects. Cocaine is an intensely vasoactive substance that can cause an extreme increase in blood pressure and heart rate, which can lead to death. Tolerance (i.e., increasing doses of cocaine needed to achieve euphoria) can develop very quickly. Cocaine use disorder and dependence are difficult to treat, and extended and escalating use is life-threatening. Many pioneers in the early medical use of cocaine, including Dr. Halstead, became addicted to cocaine via self-experimentation [3].

Given the acute and chronic adverse effects associated with cocaine, the search continued for a local anesthetic that would safely provide the desired anesthetic effects. In 1904, the German chemist Alfred Einhorn introduced the local anesthetic procaine, later more commonly known by its brand name, Novocain [6]. Although procaine, an ester-type local anesthetic, is no longer available in dental cartridges in the United States, "Novocain" is still used colloquially as an umbrella term for all local anesthetics. In 1948, lidocaine, an amide-type local anesthetic, was introduced by Nils Lofgren of Astra Pharmaceuticals [7]. Lidocaine is still widely used today, and for many it remains the "gold standard" of local anesthetics. Several additional local anesthetics have been developed since lidocaine was introduced, improving the ability of dental clinicians to safely provide profound local anesthesia.

CHEMICAL CLASSIFICATION OF LOCAL ANESTHETICS

The pharmacologic properties of local anesthetics are directly related to their molecular structure. The basic chemical structure of a local anesthetic consists of an aromatic ring (which enhances lipid solubility) and an intermediate ester or an amide chain and a terminal amine [8]. As such, all of these agents are classified as either an ester type or an amide type.

Procaine is an ester-type local anesthetic, as is the topical anesthetic benzocaine. However, the injectable local anesthetics commonly used in dentistry today are all classified as amides, including articaine, bupivacaine, lidocaine, mepivacaine, and prilocaine. Although articaine is technically classified as an amide-type local anesthetic, it is the only one that contains a thiophene (sulfur-containing) ring and an additional ester ring [9; 46].

Amide-type local anesthetics have the same basic chemical structure of the ester types, but with an intermediate amide group (rather than an ester) and a terminal amine that enhances water solubility. The ability to obtain profound intraoral anesthesia is facilitated with the use of amide formulations compared with ester formulations, and as noted, they are greatly favored in the United States [11]. The risk of an allergic reaction is also significantly lower with amide-type local anesthetics compared with ester-types, but the amide-type has a slightly greater risk of systemic toxicity, usually dose related. The positive attributes of amide-type local anesthetics outweigh the potential for adverse systemic effects.

THE PHYSIOLOGY OF LOCAL ANESTHETICS

Local anesthetics used in dentistry induce a temporary loss of sensation in the various divisions of the maxillary and mandibular branches of the trigeminal nerve (i.e., cranial nerve V). Local anesthetics prevent the generation and propagation of nerve impulses in response to painful stimuli from procedures such as oral or periodontal surgery, restorative dentistry, or endodontic treatment.

Neurons are the basic structural cell of the nervous system and can be broadly categorized as either primary sensory (afferent) or motor (efferent). Sensory neurons are responsible for the transmission of sensory impulses, including painful stimuli, to the central nervous system (CNS). These neurons have three major components: the dendrites, the axon, and the cell body. The dendrites, also referred to as the peripheral process, are composed of branched terminal endings of the nerve that propagate stimulation received from other cells and conduct an impulse to the CNS. The impulse continues along the axon, a cable-like, myelinated structure that conducts the message to the brain or spinal cord. While an axon may appear to be a continuous, uninterrupted structure, there are small gaps in the myelin sheath at intervals of about 1 mm, known as nodes of Ranvier. The cell body is not involved in the transmission of neural impulses but functions to provide the metabolic needs of the neuron. The terminal endings of the axon form synapses with various nuclei of the CNS for the interpretation of the initial stimulus.

The propagation of an impulse along a neuron is an electrochemical event. Various concentrations of sodium, potassium, and chloride ions in the extracellular fluid that surrounds the axons and the axoplasm leave the interior of the axon with a negative electric potential of -70 mV when the neuron is in its resting state [12]. When the receptors in the peripheral zone perceive a stimulus, the initiation of a nerve impulse begins with a rapid increase of axon membrane permeability, a process known as depolarization. This features opening of sodium channels in the axon membrane that allow for an influx of sodium ions and a temporary reversal of the electric potential of the axon; the interior of the axon acquires an electric potential of +40 mV [13]. Repolarization returns the neuron to its normal resting electric potential. The process begins anew when a subsequent stimulus is encountered.

Local anesthetics exert their effect by binding to the intracellular surfaces of the sodium channels [14]. This action blocks the influx of sodium ions into the interior of the axon, which prevents depolarization of the axon and inhibits a sensory nerve impulse. When the local anesthetic diffuses away from the axon, normal sensory function returns. The type of anesthetic used and the inclusion of a vasoconstrictor (e.g., epinephrine) will influence the duration of this action. Certain factors, such as the presence of active infection in the area to be anesthetized, heightened patient anxiety, or inaccurate deposition of the agent, may affect the ability of a local anesthetic to achieve the appropriate level of anesthesia.

LOCAL ANESTHETIC AGENTS

Before any use of a local anesthetic, it is imperative to complete a review of the patient's medical history. Patients who report a history of adverse systemic effects after receiving an injection of a local anesthetic should be questioned as to the nature of the problem and the manner by which it was resolved. If necessary, previous clinicians should be contacted to determine the dose of the anesthetic used, whether the reaction was immediate or delayed, and the medical intervention required.

Though local anesthetic injections are very commonly used for dental procedures, it is important not to be complacent. Errors in injection technique can lead to an intravascular injection, which can cause adverse effects such as seizures and cardiovascular events. While serious adverse systemic effects are rare, careful injection technique can minimize their occurrence. Clinicians should always have the training and the equipment available to provide an immediate response in the event that a medical emergency develops after the injection of a local anesthetic or any other acute medical problem.

VASOCONSTRICTORS

The local anesthetics discussed in this section are all amide-type local anesthetics. As a group, these medications are classified as vasodilators. However, vasodilation in an area in which a local anesthetic is deposited is undesirable, as increased blood flow will expedite the elimination of the drug and decrease its duration of action. There is also an increased risk of rapid systemic absorption, with a commensurate increased risk of systemic toxicity. To combat this, vasoconstrictors have been added to most local anesthetics used in dentistry. Because most local anesthetics contain a vasoconstrictor, it is essential to understand their mechanism of action, pharmacologic effects, and potential problems associated with their use.

Most commonly, the vasoconstrictor epinephrine is added in a 1:100,000 concentration. Concentrations of 1:200,000 and 1:50,000 also exist, though the latter is rarely used due to its strong sympathomimetic (stimulant) cardiovascular effects. Epinephrine in its varied concentrations is used in conjunction with all local anesthetics except mepivacaine, with which a 1:20,000 concentration of levonordefrin is used. Levonordefrin in its 1:20,000 concentration has the approximate pharmacologic potency of 1:100,000 epinephrine [15; 46]. Though the 1:100,000 concentration of epinephrine appears to offer no advantage in prolonging anesthesia compared to a 1:200,000 concentration, an improved ability to achieve hemostasis is facilitated with concentrations of 1:100,000 or greater [16].

Vasoconstrictors stimulate the contraction of the smooth muscle layer in blood vessels, which results in constriction of the blood vessels in the area and decreases the perfusion of blood. This decreased flow of blood to the anesthetized area favors the retention of the local anesthetic for an increased duration, increases the depth and profundity of anesthesia, and delays the systemic absorption of the local anesthetic (thereby decreasing the potential for systemic toxicity). The ability to achieve hemostasis is also facilitated when vasoconstrictors are included in local anesthetic solutions.

There has been concern about the use of epinephrine in patients with hypertension or ischemic heart disease due to the stimulant cardiovascular effects. The ability to obtain deep and prolonged anesthesia with the inclusion of epinephrine can minimize the potential for breakthrough pain during a dental procedure, thus minimizing the potential for a pain-related increase in blood pressure. In one study, the use of one to two cartridges of lidocaine with 1:100,000 epinephrine in the dental treatment of patients with cardiovascular disease was associated with a low frequency of adverse cardiovascular events [17]. Other studies have shown that the benefits of the extended duration of anesthesia associated with the co-administration of epinephrine are greater than the risk of a hypertensive crisis or cardiovascular problems during dental treatment [18]. However, caution is advised in applying the results of these studies to all patients with hypertension or cardiovascular disease, as the degree of morbidity can vary considerably. Vital signs should be taken before the administration of local anesthesia and ideally monitored during treatment. Dental treatment should be deferred in cases of elevated blood pressure. If there is any concern about the ability of a patient with hypertension or cardiovascular disease to tolerate the use of a local anesthetic with a vasoconstrictor, the patient's physician should be consulted first.

Epinephrine is an endogenous hormone produced by the adrenal gland and is an important component of the "fight-or-flight" response. An allergy to epinephrine is not possible given its production in the body. However, an inadvertent intravascular injection of a local anesthetic containing epinephrine can produce untoward symptoms such as tachycardia, heart palpitations, chest tightness, anxiety, and diaphoresis. If these symptoms emerge, the patient should be seated in an upright position and monitored closely until they resolve, usually within a few minutes. Symptoms that worsen require emergency medical treatment by the staff and contact of emergency medical services.

There are relatively few absolute contraindications to the use of epinephrine in local anesthetics. Patients with unstable angina, refractory arrhythmias, untreated or uncontrolled hypertension, or uncontrolled hyperthyroidism should not receive any elective dental treatment until they are medically stabilized. Epinephrine is also contraindicated in patients with pheochromocytoma, a tumor of the medulla of the adrenal gland that results in hypersecretion of endogenous epinephrine, with subsequent elevated blood pressure [19]. Emergency dental procedures for these patients should be performed in a hospital or an outpatient hospital center.

The life span of epinephrine and levonordefrin is extended by the inclusion of antioxidants such as sodium metabisulfite in the local anesthetic solution, and patients with an allergy to sulfites may experience an allergic reaction to the sodium metabisulfite preservative. These patients should be treated with an anesthetic that does not contain a vasoconstrictor in order to avoid a systemic allergic response [49].

LIDOCAINE

Since its introduction in 1948, lidocaine has become the most commonly used local anesthetic in the United States and remains the "gold standard" to which all other local anesthetics are compared [13]. It is available without epinephrine and with 1:50,000, 1:100,000, and 1:200,000 concentrations of epinephrine. As noted, the formulation with 1:100,000 epinephrine is used most frequently. Lidocaine is available in a 2% formulation in a 1.7-mL cartridge (containing 34 mg lidocaine) or a 1.8-mL cartridge (containing 36 mg lidocaine). The maximum recommended dose (MRD) of 2% lidocaine for adults and children older than 12 years of age is 7 mg per kg of body weight, to a maximum of 300 mg. Children younger than 12 years of age should receive a maximum of 4.5 mg per kg of body weight up to 100–150 mg [14]. The lowest possible dose of 2% lidocaine to provide the anesthesia required should be used, and the MRD should rarely be attained. During full-mouth extractions or full-mouth restorative rehabilitation, it is important to keep an accurate record of the number of cartridges used.

The onset of anesthesia for 2% lidocaine with 1:100,000 epinephrine is about five minutes, with a duration of approximately one hour for pulpal anesthesia and three to five hours for soft tissue anesthesia [46]. Amide-type anesthetics like lidocaine are metabolized by the liver and excreted by the kidneys, so the presence of hepatic and/or renal disease can compromise metabolism. For patients with these conditions, consultation with the patient's physician may be necessary in order to determine the dose of lidocaine that can be metabolized and excreted safely under these conditions. The 2% lidocaine formulation with 1:50,000 epinephrine should not be used for patients with hypertension or cardiovascular disease given the enhanced stimulant effect; a lower epinephrine concentration should be used [21].

ARTICAINE

Articaine is the most recent addition to the dental local anesthetic market in the United States. Although it has been used in Germany since 1976, approval for use in the United States was granted in 2000 [22; 23]. Initial approval of articaine was delayed because it contained the banned preservative methylparaben [24]. Sodium metabisulfite is now used as the preservative in articaine plus epinephrine, so use of this local anesthetic should be avoided in patients with sulfite allergies.

Articaine is available in a 4% formulation in 1.7-mL cartridges with 1:100,000 or 1:200,000 epinephrine concentration; one cartridge contains 68 mg of articaine. Although articaine is classified as an amide-type local anesthetic, as discussed, it has a unique chemical structure, with a thiophene ring and an additional ester ring [25; 46; 59]. The thiophene ring increases the lipid solubility of articaine and promotes faster absorption though the lipid component of the neuron membrane. This should translate to a faster onset of anesthesia compared with other amide-type local anesthetics, but studies have been conflicting [26; 27; 28]. Some studies have suggested that there is no significant difference in the onset of anesthesia of articaine and other local anesthetics, such as lidocaine and prilocaine [26]. One study suggested that articaine did have a faster onset of anesthesia when compared with lidocaine, and other studies have suggested that a faster onset of anesthesia with articaine was found with anterior but not posterior teeth [27; 28; 58]. Given the variable results of these studies, it cannot be stated with scientific certainty that the onset of anesthesia of articaine is faster than that of lidocaine or prilocaine.

The ester side chain also influences the way articaine is metabolized. The other amide local anesthetics are primarily metabolized in the liver. Due to the presence of the ester side chain, approximately 90% to 95% of articaine is metabolized in the plasma by plasma carboxylesterase, with only about 5% to 10% undergoing metabolism by the liver [29]. Because the metabolism of articaine has minimal reliance on hepatic metabolism, it is the anesthetic of choice for patients with compromised liver function, including those with hepatitis C or cirrhosis. Articaine plasma metabolism is much quicker than the hepatic metabolism of other amide-type local anesthetics, resulting in a shorter half-life (20 minutes) compared with lidocaine (90 minutes) [8]. In lengthy dental procedures, when additional doses of a local anesthetic are required, the expedited clearance of articaine minimizes the occurrence of an accumulation of toxic levels of this anesthetic.

The onset of infiltration anesthesia for articaine with 1:100,000 or 1:200,000 concentration of epinephrine is approximately one to two minutes, and the onset for anesthesia with a mandibular block is two to three minutes for articaine with a 1:200,000 concentration of epinephrine [13]. There does not appear to be a significant difference in the duration of pulpal anesthesia between articaine with 1:100,000 or 1:200,000 concentration of epinephrine [57]. The 1:200,000 concentration is preferred for patients with hypertension or cardiovascular disease.

The MRD of articaine for adults is 7 mg per kg of body weight up to 500 mg per appointment. Children older than 4 years of age have an MRD of 5 mg per kg, significantly lower than the allowed maximum for adults [30]. Clinicians who rarely treat children should be cognizant of this difference to avoid using a toxic dose. This anesthetic is not recommended for children younger than 4 years of age.

Articaine has an exceptional ability to penetrate dense cortical bone to the extent that some studies have noted that maxillary buccal infiltration has produced anesthesia on the corresponding palatal area without the need for a separate injection for the palate, although this needs to be replicated in future studies [31; 32]. There are also some concerns that articaine's 4% solution may confer a higher risk of prolonged paresthesia or anesthesia following blocks of the inferior alveolar (mandibular) nerve, and reports on this issue have been conflicting. Mitigating factors, such as nerve damage during the surgical removal of mandibular molars (especially third molars) or direct trauma from the needle striking the inferior alveolar nerve during an injection, can also result in prolonged anesthesia or paresthesia.

International studies have observed an increase in nerve injuries the year after articaine was introduced [33]. However, a retrospective study in the United States that analyzed data of patients with nerve dysfunction following an injection of a local anesthetic did not duplicate these data. In this analysis, lidocaine was used in 35% of cases of nerve dysfunction, compared with articaine, which was used in 30% of cases [34]. Clinicians should keep abreast of new studies and developments to determine if the use of articaine is appropriate for their patients.

BUPIVACAINE

Bupivacaine has been available in cartridge form in the United States since 1983 [13]. Bupivacaine is an analogue of mepivacaine, another amide-type of local anesthetic, but with a fourfold increase in potency and toxicity [21]. Bupivacaine is only available in a 0.5% formulation with a 1:200,000 concentration of epinephrine. Bupivacaine binds strongly to sodium channel proteins, which causes a protracted closing of these channels and prevents initiation and propagation of nerve impulse for an extended time, resulting in a prolonged anesthetic effect [35]. It takes 6 to 10 minutes for the onset of anesthesia, which is the slowest of all amide anesthetics. As such, this is not the anesthetic of choice for short-to-intermediate dental procedures. It also has the longest duration of both pulpal and soft tissue anesthesia, making it an ideal anesthetic for lengthy restorative procedures and to prevent post-surgical emergence of pain. After an inferior alveolar nerve block, the duration of pulpal anesthesia is approximately 1.5 hours; the duration of soft tissue anesthesia can extend up to 12 hours [20; 35].

While the extended duration of anesthesia is desirable for certain cases, it can also increase the potential for iatrogenic tissue trauma (i.e., patients accidentally biting anesthetized soft tissue of the lip, cheek, or tongue). Bupivacaine should not be used in patients who have poor neuromuscular control, including those with Parkinson disease, residual neuromuscular coordination problems due to cerebral palsy or stroke, or the advanced stages of degenerative neuromuscular diseases such as multiple sclerosis. Similarly, patients with cognitive impairment that precludes their ability to comprehend and remember post-operative instructions may also have an increased potential for soft tissue damage when anesthesia is extended.

A 1.8-mL cartridge of 0.5% bupivacaine contains 9 mg of the drug. The MRD of bupivacaine for adults and children 12 years of age and older is 90 mg per appointment, or 10 cartridges. Although 10 cartridges is allowable, this is a large dose and clinicians should strive to use the minimum dose necessary to provide the appropriate depth and duration of anesthesia required for the procedure. Bupivacaine is not recommended for patients younger than 12 years of age [14; 59]. Because bupivacaine preparations include a 1:200,000 concentration of epinephrine, the considerations outlined for this vasoconstrictor should also be taken into account.

PRILOCAINE

Prilocaine first entered the U.S. dental market in 1971 [36]. It is currently available in a 4% formulation with a 1:200,000 concentration of epinephrine. Because prilocaine is associated with fewer vasodilation properties than lidocaine, it is also available plain, with no vasoconstrictor. Prilocaine plain is ideal for patients who have allergies to sulfites, as it is free of sodium metabisulfite.

The time for onset of anesthesia and duration of pulpal and soft tissue anesthesia vary depending on the affected arch (maxillary or mandibular), whether infiltration or an inferior alveolar nerve block was used, and whether the plain formulation or the formulation including epinephrine is used. When prilocaine plain is used for maxillary teeth, the onset of anesthesia is two to three minutes, with a duration of pulpal anesthesia of about 15 minutes and soft tissue anesthesia of about 1 to 1.5 hours. When prilocaine with 1:200,000 epinephrine is used for the maxillary teeth, the onset of anesthesia is about 2 minutes, with a duration of pulpal anesthesia of about 45 minutes and a duration of soft tissue anesthesia of approximately 2 hours. When anesthesia

for mandibular molars requires blocking the inferior alveolar nerve, the onset of anesthesia for prilocaine plain is 5 minutes or more, with the duration of pulpal anesthesia being 1 to 1.5 hours while soft tissue anesthesia may extend to 2.5 hours. When prilocaine with 1:200,000 epinephrine is used for anesthetizing mandibular molars by the nerve block, the onset of anesthesia ranges between two to four minutes. In this case, the duration of pulpal anesthesia is approximately 1.5 hours, while soft tissue anesthesia can extend to 3 hours. Prilocaine plain is suitable for shorter procedures, and prilocaine with 1:200,000 epinephrine can be used for short and intermediate dental procedures [37; 46].

Each 1.7-mL cartridge of prilocaine contains 68 mg of the active anesthetic. The MRD of both forms of prilocaine is 6 mg per kg of body weight for adults, with a maximum cumulative dose of 400 mg, or less than six cartridges per appointment (defined as a two-hour period) [13; 59].

As with the 4% articaine solution, concerns regarding the potential for neurotoxicity have also been raised about 4% prilocaine. Studies exploring the relationship between the use of 4% prilocaine for inferior alveolar (mandibular) nerve blocks and the subsequent development of an oral paresthesia of the lip and/or tongue reveal that there is a very slightly increased risk. A 2010 report reviewed 10 years of U.S. cases of oral paresthesia involving articaine, bupivacaine, lidocaine, mepivacaine, and prilocaine [38]. The overall incidence of oral paresthesias for all local anesthetics was one case per 13.8 million cartridges used. Prilocaine alone was associated with an incidence of one case of oral paresthesia for every 2 million cartridges used [38]. A 2015 analysis of the U.S. Food and Drug Administration Adverse Event Reporting System showed similar results, with prilocaine having the greatest association with paresthesia [60]. While the risk of an oral paresthesia after the use of prilocaine for mandibular blocks is small, it is greater than the composite risk of all of the other amide-type anesthetics combined.

Prilocaine is also associated with a rare but potentially serious problem called methemoglobinemia. (This complication is also theoretically possible with articaine and benzocaine, but no cases have been reported with appropriate dental use.) This can occur due to congenital errors of metabolism or by the use of medications that increase plasma concentrations of methemoglobin. Methemoglobin is a variant of hemoglobin that is incapable of binding oxygen, and methemoglobinemia is diagnosed when red blood cells contain more than 1% methemoglobin [8]. A metabolite of prilocaine, *o*-toluidine, can stimulate the formation of methemoglobin, potentially to the point of toxicity. This problem is unlikely to occur when the MRD of prilocaine is not exceeded.

Patients will become symptomatic when the proportion of methemoglobin exceeds 10% to 15% [39]. Cyanosis is usually evident in the nail beds and the lips; other symptoms include fatigue, shortness of breath, and mental status changes. Patients who develop methemoglobinemia require intravenous administration of methylene blue to reverse the problem [36]. Supplemental oxygen is not useful, as methemoglobin does not carry oxygen. Hereditary methemoglobinemia is an absolute contraindication for the use of prilocaine.

Prilocaine is metabolized by the liver and excreted by the kidneys. If hepatic or renal disease is present, the patient's physician should be consulted about the ability to use this agent or the need to adjust the dose.

Lidocaine/Prilocaine Combination

In 2003, a needle-free combination of lidocaine 25 mg/g and prilocaine 25 mg/g in a gel formulation was approved for dental use [40]. These local anesthetics are combined in preloaded cartridges and are introduced circumferentially around the gingival sulcus of a tooth that is to undergo a root planing and scaling procedure. The onset of anesthesia is 30 seconds and the duration is approximately 20 minutes. The intent is to provide local anesthesia for

the contiguous periodontal tissues without residual numbness of the lip, tongue, or cheek. This formulation is considered a local anesthetic that is applied subgingivally (rather than a topical anesthetic). Lidocaine/prilocaine (brand name Oraqix) is available in 1.7-g cartridges. The MRD per appointment is 8.5 grams, or five cartridges [14; 59]. These are both amide anesthetics, so they undergo hepatic metabolism and renal excretion. Because prilocaine is a component of this formulation, it should not be used in patients with a history of hereditary methemoglobinemia.

MEPIVACAINE

Mepivacaine is available in two distinct formulations in the United States. Because it produces less vasodilation, it is available with no vasoconstrictor as 3% plain or in a 2% formulation with 1:20,000 levonordefrin.

Mepivacaine 3% Plain

Mepivacaine 3% plain is available under several brand names in 1.7-mL cartridges. It was originally approved in 1960 for use as a local anesthetic in dentistry [41]. The onset of anesthesia is similar to that of lidocaine. When mepivacaine 3% is used for a block of the inferior alveolar (mandibular) nerve, the duration of pulpal anesthesia is 40 minutes; this reduces to only about 20 minutes when used for infiltration anesthesia. Soft tissue anesthesia lasts approximately three hours when the mandibular block is utilized and about two hours when administered via infiltration [42]. As such, this anesthetic is ideal for procedures of short duration.

The MRD of mepivacaine 3% plain for children younger than 10 years of age is 5–6 mg per kg of body weight, with an absolute maximum of 270 mg per appointment. Adults and children older than 10 years of age may be dosed a maximum of 6.6 mg per kg of body weight, up to 300 mg [14]. Given that each cartridge contains 51 mg of active anesthetic, no more than five to six cartridges should be used [13; 59].

As with all local anesthetics, the lowest cumulative dose possible should be used to achieve anesthesia and complete the dental procedure. This is particularly essential when mepivacaine 3% plain is used in children. The short duration of 3% mepivacaine minimizes the potential for traumatization of anesthetized soft tissue; however, it is 1.5 times more toxic than the 2% formulation [43]. Therefore, the use of mepivacaine 3% plain in children, especially those younger than 5 years of age, should be administered via infiltration and restricted to the smallest dose whenever possible.

Mepivacaine 3% plain undergoes metabolism in the liver and is excreted by the kidneys, so an adjustment of the dosage may be required in the presence of hepatic or renal disease.

Mepivacaine 2% with 1:20,000 Levonordefrin

The 2% formulation of mepivacaine is the only amide-type anesthetic in the United States that uses levonordefrin as the vasoconstrictor rather than epinephrine. In a formulation of 1:20,000, levonordefrin is 5 times more concentrated than 1:100,000 epinephrine and 10 times more concentrated than epinephrine in a 1:200,000 concentration. Like epinephrine, levonordefrin has stimulant effects on the cardiovascular system (i.e., elevates systolic and diastolic blood pressure and mean arterial pressure), so it should be used with caution in patients with cardiovascular disease and/or hypertension [44; 59]. The physiologic effects of levonordefrin are similar to those of norepinephrine, another catecholamine that is secreted by the medulla of the adrenal gland.

Mepivacaine 2% with 1:20,000 levonordefrin has a depth and duration of pulpal and soft tissue anesthesia that is similar to lidocaine with 1:100,000 epinephrine; however, it does not provide the same degree of hemostasis [45]. As such, this is not the anesthetic/vasoconstrictor of choice for oral or periodontal surgical procedures, especially those involving multiple teeth or quadrants.

The addition of 1:20,000 levonordefrin extends the duration of anesthesia compared with 3% mepivacaine plain. Pulpal anesthesia lasts approximately 1.5 hours after inferior alveolar (mandibular) nerve block and approximately 1 hour after infiltration administration for maxillary teeth. Soft tissue anesthesia extends to approximately five hours after a mandibular block and approximately three hours after infiltrative administration [42; 46].

Mepivacaine 2% with 1:20,000 levonordefrin is available in 1.7-mL cartridges, with 34 mg of mepivacaine per cartridge. The MRD for adults is 400 mg mepivacaine per appointment, and the maximum pediatric dose per appointment is 6.6 mg per kg of body weight or 180 mg, whichever is less [14; 59].

Elevated blood pressure can occur at doses that are well below the MRD, and clinicians should keep in mind that excessive blood plasma levels of levonordefrin can produce an adverse cardiovascular event. The inclusion of levonordefrin requires the addition of a preservative (e.g., sodium metabisulfite); patients with a sulfite allergy can be administered 3% mepivacaine plain, but the 2% formulation should be avoided.

ADJUNCTIVE MEDICATIONS

Many patients fear that injections of a local anesthetic will be painful, and this is one of the reasons that people may defer necessary dental treatment. In addition, patients may complain about the awkward feeling of residual "numbness" following the administration of local anesthetic that can temporarily interfere with eating, speaking, and swallowing. Medications are available to minimize the discomfort associated with injections of local anesthetics and hasten the return to "normal" feeling of tissues that were anesthetized.

TOPICAL ANESTHETICS

Topical anesthetics may be used to minimize the pain associated with the initial penetration of the anesthetic needle. These agents are available as gels, sprays, or muco-adherent patches and are an excellent means to increase patient comfort during an injection procedure. Because these medications undergo systemic absorption, they should not be applied to areas in which the tissue is ulcerated and/or highly inflamed. The most frequently used options include benzocaine and lidocaine.

Benzocaine

Benzocaine gel in a concentration of 20% is the most common topical anesthetic used in dentistry. It is marketed under several brand names and is available in many flavors to enhance patient acceptance. Benzocaine is not water-soluble, so it must be combined with other substances (e.g., alcohol, propylene glycol, polyethylene glycol) in order to make it suitable for application to the oral mucosa [13]. The tissue of the intended injected site should be isolated and dried prior to the application of benzocaine, as salivary contamination can dilute the drug and negate its effectiveness.

Benzocaine 20% formulations penetrate the oral mucosa to a depth to 2–3 mm and minimize the sensation of the initial insertion of the needle. Benzocaine 20% is also available in a liquid spray formulation, but this application can make it difficult to control the amount used and lacks the tissue adherence of the gel formulations. This will minimize the anesthetic effect and can also result in patients swallowing the topical preparation, causing transient anesthesia of the pharyngeal region and difficulty in speaking and swallowing. Inhalation of a spray of benzocaine 20% that is misdirected toward the oropharynx can lead to potentially serious problems such as laryngospasm.

Ester-type local anesthetics and articaine (because of its additional ester ring) are associated with a higher incidence of allergic reactions because their metabolism yields a p-aminobenzoic acid (PABA) metabolite [10]. Inflammation or ulceration at the site of benzocaine application suggests a hypersensitivity reaction and requires the use of an alternative topical anesthetic. If a patient displays a hypersensitivity reaction to topical benzocaine, articaine should not be used due to the potential for cross-sensitivity. If a flavored topical anesthetic is used, care should be taken to ensure that patients (particularly children) do not ingest the formulation. As noted for prilocaine, methemoglobinemia is a rare but potential adverse effect of benzocaine use, especially when used in the spray formulation in children [11].

Topical benzocaine 20% has the same mechanism of action as injectable local anesthetics. It decreases the neuron membrane permeability to sodium ions, thus blocking the initiation and conduction of a nerve impulse. However, the area involved and the duration of action are much less than that of an injectable anesthetic. As with all anesthetics, the smallest possible dose of benzocaine 20% should be used. Patients with a history of allergic reaction to ester formulations or hereditary methemoglobinemia should use an alternative topical anesthetic.

Lidocaine

Lidocaine is used as both an injectable and a topical anesthetic. Topically, it is available as a 2% or 5% gel, 2% solution, 4% or 5% solution, 5% ointment, or 10% spray [61]. Lidocaine 5% topicals have a similar potency to 20% benzocaine; however, its onset of action is more delayed, requiring at least three minutes to achieve adequate anesthesia. It is effective on alveolar mucus but not on the palatal mucous membrane [61].

REVERSAL AGENTS

The ability to maintain prolonged anesthesia after the completion of oral or periodontal surgery and endodontic therapy is essential. However, many procedures, including basic restorative procedures, do not require extended anesthesia. When protracted anesthesia is not required, an extended period of "numbness" in the lip, tongue, and cheek can make basic functions such as masticating, speaking, and swallowing difficult and can increase the risk of iatrogenic soft tissue damage (i.e., biting oral soft tissues that remain anesthetized). This can be a special concern among children and patients with acquired or congenital neuromuscular diseases or muscle control problems.

In 2008, phentolamine mesylate, an anesthetic reversal agent, was approved for dental use in the United States [47]. Originally developed in the 1950s to decrease elevated blood pressure associated with pheochromocytoma, phentolamine mesylate is classified as a vasodilator [48]. It is supplied in 1.7-mL cartridges under the brand name OraVerse and is the only reversal agent available for local anesthetic agents used in dentistry. Each cartridge contains 0.4 mg of the drug. In adults, dosing is dependent on the number of cartridges of anesthetics used; 0.2 mg of phentolamine mesylate should be administered for each one-half cartridge (i.e., 0.4 mg per one cartridge). Phentolamine mesylate acts as an alpha-adrenergic receptor antagonist that competes with vasoconstrictors (e.g., epinephrine) for the same receptor sites [59]. This results in decreased vasoconstriction and more vasodilation, which promotes an expedited uptake of the local anesthetic and a return to normal sensation for the patient.

A study published in the *Journal of the American Dental Association* evaluated the effectiveness of phentolamine mesylate in reducing the duration of anesthesia [50]. A group of 115 children between 6 and 11 years of age were divided into either a treatment group (receiving an injection of phentolamine mesylate) or a placebo group. The median time for return of normal lip sensation in the treatment group was 60 minutes; time to return to normal sensation was more than twice as long (135 minutes) in the placebo group. Of the 38 patients who had dental procedures performed on the mandibular arch, there was a 120-minute reduction in the median time that it took to regain normal sensation in the lip. The 34 patients with dental procedures completed on the maxillary arch experienced a 52.5-minute reduction in the median time that it took to regain normal sensation in the lip with the administration of phentolamine mesylate [50]. Subsequent studies have shown similar effectiveness [62].

The expedited return to normal sensation decreases the risk of iatrogenic tissue damage and facilitates the return to normal oral function. However, as with any medication, there are potential adverse effects. Injection site pain and reports of transient paresthesia have been associated with phentolamine mesylate use [14]. Because phentolamine mesylate is a vasodilator, its concurrent use with other medications that cause vasodilation can lead to an unsafe decrease in blood pressure. This includes phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) used in the treatment of erectile dysfunction and nitrates used to treat ischemic heart disease; use of these medications precludes the simultaneous use of phentolamine mesylate. Phentolamine mesylate is also contraindicated in patients who are younger than 6 years of age, who weigh less than 15 kg (33 lbs), who have a history of angina or myocardial infarction, or who have a known hypersensitivity to phentolamine mesylate [42]. The initial use of phentolamine mesylate as an anesthetic reversal agent in dentistry has provided encouraging results. Long-term studies and continued research are essential to determine if any problems or contraindications emerge with its continued use.

BUFFERING LOCAL ANESTHETIC SOLUTIONS

Pain that patients perceive after the initial penetration of the needle can be caused by advancement of the needle through the tissue layers (especially while blocking the inferior alveolar nerve of the mandibular arch) or pressure of the anesthetic solution against mucosal tissue that is bound tightly to the underlying bone, such as on the hard palate. However, the acidic chemical composition of the local anesthetic solution may also cause pain.

Local anesthetic solutions that are "plain" (no vasoconstrictor) have a pH of approximately 5.9, while those containing epinephrine or levonordefrin have a pH of approximately 3.5, which classifies these as solutions with weak-to-moderate acidity [51]. The "sting" or "burning" patients feel during the injection of a local anesthetic is a result of this acidity. This may also account for post-injection soft tissue trauma. Manufacturers have addressed this issue by developing a system to increase the pH of a local anesthetic solution to increase patient comfort and minimize the potential for acidity-related soft tissue trauma after the injection.

Local anesthetic solutions are combined with an acid (hydrogen chloride) to form a salt (hydrochloride) to facilitate water-solubility. The additional use of sodium metabisulfite in solutions with vasoconstrictors further decreases the pH. A chairside system has been developed by which an 8.4% sodium bicarbonate solution can be mixed with a standard cartridge of a local anesthetic solution to increase the pH. A mixing pen is used to transfer some of the 8.4% sodium bicarbonate solution from a separate cartridge into the 1.8- or 1.7-mL local anesthetic cartridge, with a connector used to secure the two cartridges together during the transfer process [52]. The chemical interaction between the sodium bicarbonate and the hydrochloride of the local anesthetic solution produces both carbon dioxide and water.

The use of this buffering system increases the pH of lidocaine with epinephrine from 3.3 (moderate acid) to 7.4 (weak base) and also increases the amount of ionized anesthetic available to penetrate the neuron [53; 49]. This allows for a more comfortable injection and promotes a faster onset of anesthesia.

Initial results from the use of this system are encouraging. However, research and long-term studies are needed to further explore the advantages and disadvantages of this system. The initial and recurring cost associated with use of this system may be offset by the ability to obtain profound anesthesia more quickly and with less pain, potentially allowing the clinician to treat more patients.

TREATMENT OF LOCAL ANESTHETIC-INDUCED MEDICAL EMERGENCIES

Although local anesthetics are generally safe, medical emergencies can occur with their use. Therefore, all staff should have a clear understanding of possible adverse events and how they can be safely managed.

Although vasoconstrictors should be avoided in patients with sulfite compound allergy, they usually play an important role in minimizing the rapid systemic dissemination of the local anesthetic. Both epinephrine and levonordefrin constrict blood vessels in the injection area, resulting in a slower systemic absorption and decreasing the chance of systemic toxicity. Aspirating before injecting slowly also minimizes the chance that the local anesthetic will be injected directly into a blood vessel, decreasing the rate of systemic circulation. Direct intravascular injection of an entire cartridge of a local anesthetic can have adverse effects on both cerebral and cardiac tissues.

The prevention of toxicity from local anesthetics involves more than a careful injection technique. A patient's age, weight, medical conditions, and current medications can all influence the metabolism and clearance of local anesthetics. The most common cause of local anesthetic toxicity is an overdose of the medication relative to the age and weight of the patient. This occurs most often in pediatric patients, but excessive doses can occur in adults, particularly elderly individuals [54]. Some local anesthetics, such as bupivacaine, are not recommended for use in patients younger than 12 years of age. Children do not have the capability to metabolize and excrete local anesthetics as well as healthy adults. In addition, the elderly, adults with low body weight, and those with chronic illness(es) may have a diminished capacity to metabolize and excrete local anesthetics. Clinicians should avoid using the same dose on each patient without regard to these factors.

Systemic disease can also affect an individual's ability to metabolize and excrete local anesthetics. Amide-type local anesthetics undergo metabolism primarily in the liver and excretion is via the kidneys. Diseases such as hepatitis and cirrhosis can adversely affect hepatic function and decrease the liver's ability to metabolize these anesthetics; a dose that is usually appropriate for the age and weight of a healthy patient can gradually accumulate to toxic levels. Patients with impaired renal function, especially those with end-stage renal disease and those on dialysis, will have difficulty excreting metabolized local anesthetics. These patients' physicians and specialists should be consulted about an appropriate dosing schedule. When multiple quadrants of restorative treatment are performed, full-mouth extractions completed, or multiple doses are administered in the same area in patients who are having difficulty achieving a state of anesthesia, the maximum allowable local anesthetic dose for the patient can be achieved quickly.

The concurrent use of certain medications can also alter the metabolism of local anesthetics. Medications such as phenytoin, meperidine, and desipramine compete with local anesthetics for the same protein binding sites, which can decrease efficacy of both drugs [13]. Cimetidine, which is in common use for the treatment of gastroesophageal reflux disease and ulcers, can decrease the rate at which lidocaine is metabolized in the liver, as both medications compete for the same hepatic enzymes [55]. These instances of competitive drug metabolism can cause a local anesthetic to be retained longer, and a toxic accumulation may be reached faster if the dose is not adjusted.

The manifestations of toxicity to local anesthetics and their vasoconstrictors can have different clinical appearances. When a local anesthetic with epinephrine is injected into a blood vessel and distributed systemically, patients may experience tachycardia, heart palpitations, and anxiety. This is usually a transient reaction that subsides in a few minutes. However, patients should be monitored to assure that it is not the beginning of a more progressive toxic reaction. Furthermore, patients should never be left alone after a local anesthetic has been injected.

Local anesthetics can cross the blood-brain barrier and can exert a depressant or excitatory action on both the CNS and the cardiovascular system. Some toxic reactions to local anesthetics can occur rapidly after the injection, while others may be delayed for several minutes. A clinically evident excitatory phase, featuring excessive talking, apprehension, and excitability, may be present during these reactions. Among the local anesthetics used, the lack of this phase occurs more frequently with lidocaine [56; 60]. Patients can progress to demonstrate signs of slurred speech, diaphoresis, nausea, vomiting, tachycardia, and an increased rate of breathing when the degree of toxicity is minimal to moderate. When higher doses of a local anesthetic cause more severe acute toxicity, the patient may develop seizures, CNS depression, hypotension, bradycardia, and a decreased respiratory rate.

When any sign of local anesthetic toxicity emerges, members of the dental care team should begin monitoring the vital signs. Fortunately, most reactions to a local anesthetic toxicity are mild and self-limiting, with only the use of supplemental oxygen needed to assist the patient. More severe reactions occur within one minute of administration of the local anesthetic and can lead to seizures and unconsciousness. When this occurs, one staff member should contact emergency medical services while the dentist and others are monitoring the airway, breathing, and circulation of the patient. If the patient has seizures that do not appear to be decreasing in intensity, a benzodiazepine may be used. The dental staff should stabilize the patient until emergency help has arrived. In rare cases, this may involve the administration of cardiopulmonary resuscitation and/or the use of an automated external defibrillator. An analysis should be completed to determine the cause of the toxic reaction so recurrence can be prevented.

CONCLUSION

This course has provided an overview of the local anesthetics used in dentistry today. These injectable medications have an outstanding safety record and consistent efficacy in achieving anesthesia. Although local anesthetics are widely used, clinicians should avoid becoming complacent about their use; adverse reactions can occur. Clinicians should not hesitate to consult with the patient's physician or specialist if there is any underlying medical condition that could challenge the patient's ability to receive, metabolize, or excrete a local anesthetic. Consideration of all aspects of the use of local anesthetics allows them to be used in a way that minimizes the potential for an untoward event while maximizing the comfort and safety of the patient.

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