Local Anesthesia Reversal

Author: Stanley F. Malamed, DDS

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LEARNING OBJECTIVES

AFTER READING THIS ARTICLE, THE INDIVIDUAL WILL LEARN:

• The types of local anesthesia and mechanisms of action
• The clinical use of a new agent that reverses soft tissue anesthesia.

ABOUT THE AUTHOR

Dr. Malamed is a professor of anesthesia and medicine at the School of Dentistry at the University of Southern California. He graduated from New York University College of Dentistry in 1969. He then completed a dental internship and residency in anesthesiology at Montefiore Hospital and Medical Center in the Bronx, NY before serving for 2 years in the US Army Dental Corps at Ft. Knox, Kentucky. In 1973, he joined the faculty of the University of Southern California School of Dentistry (Los Angeles) where today he is a professor of anesthesia and medicine. He is also a Diplomate of the American Dental Board of Anesthesiology. He has authored more than 120 scientific papers and 16 chapters in various medical and dental journals and textbooks in the areas of physical evaluation, emergency medicine, local anesthesia, sedation, and general anesthesia. He authored the textbooks Handbook of Local Anesthesia (5th ed.), Emergency Medicine in Dentistry (6th ed.), and Sedation: A Guide to Patient Management (4th ed.). He can be reached at (213) 740-1081 or malamed@usc.edu.

Disclosure: Dr. Malamed is a paid consultant for Novalar Pharmaceuticals, Inc.

INTRODUCTION

Local anesthesia (LA) forms the backbone of pain control techniques in dentistry. The introduction of lidocaine hydrogen chloride (HCl) in 1948 led to an explosion of new drugs that have provided the dentist and dental patient with the opportunity to experience both pain-free treatment and a pain-free post-treatment period. However, many patients complain that lingering numbness of residual soft-tissue anesthesia (STA) following completion of a dental procedure is inconvenient, uncomfortable, and can lead to soft-tissue injury due to the inability to detect pain, especially in children.

This article reviews the types of LA and mechanisms of action, and discusses a new agent that reverses STA.

The LA armamentarium today consists of drugs providing a range of durations of pain control, from short-acting drugs (~30 minutes pulpal anesthesia) to long-acting drugs providing pulpal anesthesia up to 7 hours and STA of up to 12 hours’ duration. Short-duration drugs provide pulpal anesthesia for approximately 30 minutes and include mepivacaine HCl 3% and prilocaine HCl 4%. The long-duration category consists of bupivacaine HCl 0.5% with epinephrine 1:200,000, providing pulpal anesthesia for up to 7 hours (commonly from 90 to 180 minutes) with STA for up to 12 hours. Interestingly, bupivacaine HCl is a long-acting anesthetic when administered by nerve block (NB) (eg, inferior alveolar NB) only. It is not nearly as long acting when administered by supraperiosteal (infiltration) injection.

As the usual length of dental treatment is approximately 44 minutes, the short-duration anesthetics fail to meet the pain control needs of many patients. The intermediate-duration category is most often used. With the inclusion of a vaso depressor (epinephrine or levonordefrin [in the US]), the drugs in this group provide pulpal anesthesia of approximately 60 minutes’ duration. Intermediate-duration drugs include articaine HCl 4% with epinephrine 1:100,000 and 1:200,000; lidocaine HCl 2% with epinephrine 1:50,000 and 1:100,000; mepivacaine HCl 2% with levonordefrin 1:20,000 (with epinephrine 1:100,000 in Canada); and prilocaine HCl 4% with epinephrine 1:200,000. Table 1 summarizes these drugs based upon expected duration of pulpal anesthesia.

It is pulpal anesthesia that allows the doctor to painlessly treat the tooth. Anesthesia of the associated soft
tissues occurs hand-in-hand with pulpal anesthesia. Though necessary for many treatments such as curettage, periodontal surgery, extractions, implants, and subgingival tooth preparation, in order for these procedures to be completed painlessly, the duration of STA is considerably longer duration than that of pulpal anesthesia, averaging 3 to 5 hours in the intermediate-duration group of LAs (Table 1).

Another factor determining not just the duration of anesthesia but its extent is the choice of local anesthetic technique. For example, following a maxillary infiltration over the lateral incisor, the tooth will be anesthetized (pulpal anesthesia) along with the localized soft tissues in that area, such as those in the buccal fold and the lip. Following the anterior superior alveolar nerve block a large area on the anterior portion of the maxilla, including the lower eyelid to the lateral border of the nose to the upper lip extending from the midline to the corner of the mouth on that side, will be anesthetized.

In the mandible, where anesthesia in the adult is usually limited to nerve blocks (inferior alveolar [Gow-Gates]), large areas of STA develop along with the desired pulpal anesthesia. The anterior two thirds of the tongue, the lower lip, and cheek are left without sensation for many hours following completion of dental treatment.

Recently, new techniques (actually the reinvention of very old techniques) have been introduced which provide localized areas of pulpal anesthesia with a minimum of associated STA. These include the periodontal ligament (PDL) injection (also known as the intraligamentary injection (ILI)\(^3\) and the intraosseous injection.\(^4\) Anesthesia of the tongue or lip is essentially nonexistent following these injections.

**RESIDUAL STA**

The long duration of residual STA may be desirable following some dental treatments; examples include surgical procedures (oral surgical, periodontal, and endodontic). However, most operative dental care requires

<table>
<thead>
<tr>
<th>Table 1. Expected Durations of Pulpal and Soft Tissue Anesthesia (STA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasopressor</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>SHORT-DURATION</strong></td>
</tr>
<tr>
<td>Mepivacaine hydrogen chloride (HCl)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Prilocaine HCl</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>INTERMEDIATE-DURATION</strong></td>
</tr>
<tr>
<td>Articaine HCl</td>
</tr>
<tr>
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<tr>
<td>Lidocaine HCl</td>
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<tr>
<td>Mepivacaine HCl</td>
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<tr>
<td>Prilocaine HCl</td>
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<tr>
<td><strong>LONG-DURATION</strong></td>
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<tr>
<td>Bupivacaine HCl</td>
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profound anesthesia (pulpal) during the relatively brief treatment period while the patient is in the dental chair. Once treatment is completed there is no longer a need for continued anesthesia of the tissues, either hard or soft. However, the need for effective intraoperative pain control normally mandates the use of LA containing a vasopressor such as epinephrine or levonordefrin, which has become a routine part of dentistry.\(^5,6\) Patients are commonly discharged from the dental office with residual numbness to their lips and tongue, typically persisting for 3 to 5 hours.\(^7\)

Residual STA presents as an inconvenience or embarrassment to the patient who is unable to function normally for many hours after leaving the dental appointment. In a survey by Rafique, et al\(^8\) of patients receiving intraoral LA, the authors stated that there were several aspects of the post-LA experience that were disliked by patients, including 3 major areas—functional, sensory, and perceptual.

Functionally, the patients disliked their diminished ability to speak (lisping), to smile (asymmetric), to drink (liquid runs from the mouth), and the inability to control drooling while still numb. Sensorially, the lack of sensation was described as quite discomforting, while the perception that their body was distorted (eg, swollen lips) was equally unpleasant. For many patients these sequelae become a significant detriment to their quality of life, making it difficult for them to return to their usual activities for hours after treatment. When the dental appointment concludes at a time approaching a meal, either lunch or dinner, patients must consider whether to eat while numb or postpone their dining until the residual STA resolves.

Though not normally a significant problem, residual STA may occasionally lead to self-inflicted injury in any patient. Self-inflicted injury to soft tissues—most commonly the lip or tongue—is more apt to be noted in younger children and in mentally disabled adult and pediatric patients (Figure 1).\(^1,9\)

A study of pediatric patients by College, et al\(^9\) revealed that a significant percentage of inferior alveolar nerve blocks were associated with inadvertent biting of the lips. By age group, the frequency of trauma to the lips was 18% (< 4 years), 16% (4 to 7 years), 13% (8 to 11 years), and 7% (> 12 years) (Table 2). This can be explained by the fact that the younger patient will test (by biting) their un-numb lip—which hurts, and then test the still-numb side—which doesn’t hurt. Where the adult would normally not proceed beyond this point, the younger child may “play” with this “feeling” and continue to bite ever harder and harder, not realizing the damage that is being inflicted. Mentally handicapped adults are just as likely to incur self-inflicted soft-tissue injury. This author was surprised to learn from dentists who treat geriatric patients that another group—the geriatric patient with dementia—presents a risk of soft-tissue injury following LA injection equal to or greater than that of children and mentally challenged adults.

**HOW LAS WORK—AN OVERVIEW**

In a simplistic description of how LA\(s\) work to block nerve conduction and prevent pain, consider a dynamite stick and a fuse (Figure 2). The dynamite stick represents the brain (central nervous system); the fuse the peripheral nerve, for example the inferior alveolar nerve. When the fuse is lit...
(when the nerve is stimulated by the drill, curette, or scalpel) it burns until it reaches the dynamite, which then explodes. Similarly, when a propagated nerve impulse reaches the brain, it is interpreted by the patient as pain.

If a small portion of the fuse were to be saturated with water (Figure 3) and the fuse then lit, it would burn only up to the area where the water was placed. The flame would die out, never reaching the dynamite stick, which would not explode. If a LA solution is deposited close to a nerve it will then diffuse into that nerve (in essence saturating it). When the dental drill stimulates a tooth distal to this site (the area that is “numb”), the nerve impulse is still propagated. This impulse will travel only as far as the area of the nerve where the LA has been deposited. The nerve impulse will then die out, never reaching the patient’s brain. As long as enough water stays in the fuse—as long as enough LA stays in the nerve—the dynamite stick will not explode, nor will the painful nerve impulse reach the brain. This defines the duration of anesthesia produced by the LA drug.

LAs “stop working” in a manner akin to that of the stick of dynamite. If the unlit but water-saturated fuse were left in the open air for a period of hours, the water would evaporate into the air. When lit, the fuse would burn and the dynamite stick would explode. The body’s equivalent to evaporation is diffusion. When the volume of LA within the nerve is greater than the volume of LA outside the nerve, the process of diffusion reverses and the drug begins to leave the nerve into the soft tissues surrounding it. Individual nerve fibers are gradually unblocked, leading to the patients telling the doctor that they are “starting to feel it again.”

As the drug exits the nerve it is absorbed into capillaries which carry the LA molecules away from the injection site via the venous circulation. The greater the volume of blood flowing through the area where the LA was deposited, the more rapidly this diffusion out of the nerve will occur. This explains why “plain” LAs have a shorter duration of both soft and pulpal anesthesia than those that contain a vasopressor. LAs inherently are vasodilators. Injection of a plain LA will increase the vascularity at the injection site, allowing for a lesser volume of LA to enter into the nerve and for the more rapid expulsion of the drug back out of the nerve. Plain LAs, as a group, provide shorter duration and less profound anesthesia than anesthetics containing a vasopressor.

The addition of epinephrine or levonordefrin to the LA will produce a diminished flow of blood into the site of LA deposition. This permits a greater volume of LA to diffuse into the nerve and, as there is less blood flowing through the region, allows the LA to remain within the nerve for a longer period of time, thus providing a longer duration of more profound anesthesia.

**HOW TO DECREASE THE DURATION OF RESIDUAL STA**

Increasing the flow of blood through the site in which LA was injected facilitates a more rapid diffusion of the LA from the nerve into the cardiovascular system, thus decreasing the length of residual STA. Any technique that causes vasodilation can produce this effect.

In the 1980s the technique known as transcutaneous electrical nerve stimulation (TENS) was successful in shortening the duration of residual STA. TENS is commonly used in sports medicine and rehabilitation from soft-tissue
Electrodes are placed on the site of injury with a low frequency electric current being delivered to the area. Application of this low-frequency (2.5 Hz) electrical current to an area that has been injured recently is of benefit to the patient in 2 ways: It acts to increase tissue perfusion produced by capillary and arteriolar dilation, while simultaneously stimulating the contraction of skeletal muscle. The net effect of these 2 processes is a pumping action in the area of application of the current. Therapeutically, an one-hour treatment at a low frequency helps to decrease edema (skeletal muscle-stimulating effect), and the increased perfusion and skeletal muscle stimulation act to “cleanse” the area of tissue injury breakdown products. With electrodes placed intraorally around the site where LA was injected, it is possible to shorten the duration of STA. This technique was short-lived as it was difficult to position the electrodes intraorally and to have them adhere firmly to the moist intraoral mucous membranes.

Another approach to the question of how to minimize residual STA would be the injection of a vasodilating drug into the area of prior LA administration. In theory, this should hasten the redistribution of the LA from the nerve into the cardiovascular system, thereby decreasing the duration of residual STA.

**PHENTOLAMINE**

Phentolamine is an alpha-adrenergic receptor antagonist approved for use by the US Food and Drug Administration (FDA) in 1952 (Figure 4). Approved uses of phentolamine include: (1) diagnosis of pheochromocytoma; (2) treatment of hypertension in pheochromocytoma; (3) prevention of tissue necrosis after norepinephrine extravasation. An early use of injectable phentolamine was in the management of impotence (erectile dysfunction).

Phentolamine is a short-acting, competitive antagonist at peripheral alpha-adrenergic receptors. It antagonizes both alpha1 and alpha2 receptors, thus blocking the actions of the circulating catecholamines, epinephrine, and norepinephrine. Phentolamine also stimulates beta-adrenergic receptors in the heart and lungs.

The clinical effects of phentolamine include peripheral vasodilation and tachycardia. Vasodilation is a result of both direct relaxation of vascular smooth muscle and alpha blockade. The drug produces positive inotropic and chronotropic effects, leading to an increase in cardiac output. In smaller doses, the positive inotropic effect can predominate and raise blood pressure; in larger doses, peripheral vasodilation can mask the inotropic effect and lower blood pressure. These actions make phentolamine useful in treating hypertension caused by increased circulating levels of epinephrine and norepinephrine, as occurs in pheochromocytoma.

The effects of phentolamine in treating impotence are mediated by alpha-adrenergic blockade in penile blood vessels. The drug’s actions cause relaxation of the trabecular cavernous smooth muscles and dilation of the penile arteries, which increases arterial blood flow into the corpus cavernosa and subsequently causes an erection.

Phentolamine is administered intravenous (IV) or intramuscular but can also be injected subcutaneously to prevent local tissue necrosis when vasoconstrictor drugs extravasate. The pharmacokinetics of phentolamine are largely unknown; 10% of a parenteral dose is excreted in the urine unchanged.

**Indications and Dosage: Diagnosis of Pheochromocytoma**

Prior to the intravenous administration of phentolamine the patient is allowed to remain in a supine position until blood pressure is stabilized. Baseline blood pressure (BP) is established by taking BP readings every 10 minutes for at least 30 minutes. An IV dose of 2.5 mg phentolamine is injected. Diagnosis of pheochromocytoma is made by monitoring BP before and after the administration of phentolamine. In patients with pheochromocytoma, BP will
markedly decrease after administration of phentolamine. If a negative result is obtained with 2.5 mg, the test is repeated with a 5 mg dose. In children, a dose of 0.05 to 0.12 mg/kg is administered IV.\textsuperscript{11,13}

**Indications and dosage:** Prevention or treatment of dermal necrosis or sloughing following extravasation of catecholamines (eg, epinephrine, norepinephrine): 5 to 10 mg phentolamine (diluted with 10 to 15 mL of normal saline) is injected into the affected area within 12 hours of extravasation. Visible hyperemia and increased tissue warmth at the site are signs of effective treatment.\textsuperscript{11,14}

**Indications and dosage:** For the treatment of hypertensive emergency related to any catecholamine excess, such as interactions between MAO-inhibitors and sympathomimetic amines: Phentolamine is administered intravenously as a bolus in a dosage of 5 to 15 mg.\textsuperscript{11,15}

**Pregnancy and Lactation**
As presently used in medicine, phentolamine is categorized by the FDA as a pregnancy category C and as “Safety Unknown” for nursing mothers.\textsuperscript{1} (Pregnancy category C—animal studies show adverse fetal effect(s) but no controlled human studies or no animal or human studies; weigh possible fetal risk versus maternal benefit. Lactation category “safety unknown”—inadequate literature available to assess risk; caution advised.)

**Availability**
Phentolamine is available as a 5-mg/ml solution for parenteral administration.

**PHENTOLAMINE MESYLATE FOR THE REVERSAL OF RESIDUAL STA**

**The Clinical Trials—Adults and Adolescents**
Novalar Pharmaceuticals developed an injectable form of phentolamine mesylate (PM) formulated to terminate the numbing sensation associated with LA when it is no longer required. The product, under the proprietary name OraVerse, contains 0.4 mg PM (0.235 mg/mL) packaged in a 1.7 mL dental cartridge.\textsuperscript{11} In May 2008, the FDA approved PM, which was marketed in February 2009.\textsuperscript{16} The dental formulation of phentolamine is approximately one twentieth the concentration as that used in medicine.

Prior to receiving FDA approval, PM went through a number of clinical trials to demonstrate its safety and efficacy for this new therapeutic indication. Two Phase III, double-blinded, randomized, multicenter, controlled studies were undertaken.\textsuperscript{17} One trial studied the safety and efficacy of PM in reversing mandibular STA, and the second trial studied the safety and efficacy of PM in reversing maxillary STA. A pediatric Phase II, double-blinded, randomized, multicenter, controlled study was conducted in dental patients, aged 4 to 11 years, who had received 2% lidocaine with 1:100,000 epinephrine.\textsuperscript{18}

In FDA mandated drug trials, Phase I trials are the first stage of testing in human subjects. Normally a small (n = 20 to n = 80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff.

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (n = 20 to n = 300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients.

Phase III studies are randomized controlled multicenter trials on large patient groups (n = 300 to n = 3,000 or more, depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current “gold standard” treatment.

In the Phase III trials for this new indication for PM, patients received a LA containing a vasoconstrictor on one side of their mouths prior to a restorative or periodontal maintenance procedure. The primary endpoint was the elapsed time to the return of normal lip sensation as measured by patient reported responses to lip palpation. Secondary endpoints included the patients’ perception of altered function, sensation and appearance, and functional deficits in smiling, speaking, drinking and drooling, as assessed by both the patient and an observer blinded to their treatment.\textsuperscript{17-20} To determine the impact of functional deficits
a patient reported outcomes questionnaire (STAR) was developed (Table 3). In the mandibular study, the time to recovery of tongue sensation was also a secondary endpoint. The dental procedure had to be completed within 60 minutes of the LA injection, and the patient's lip had to still be numb at that time or that individual was excluded from the study. All 244 patients randomized in the mandibular study reported lip anesthesia at one hour, while only 194 reported that their tongues were still numb at this time. The maxillary study enrolled 240 patients.

Patients were randomized to receive one of 4 LA: 2% lidocaine + epinephrine 1:100,000; 2% mepivacaine + levonordefrin 1:20,000; 4% articaine + epinephrine 1:100,000; or 4% prilocaine + epinephrine 1:200,000. Drugs were randomized using a 6:1:1:1 ratio based on usage patterns in the United States.

At the conclusion of the treatment, the patient received either PM or a control injection. Both patients and all investigators were blinded to the treatment assigned. The study drug was administered at the same site, and in the case of PM, the same number of cartridges (one or 2) as the previous LA injection(s). The control was a sham injection in which the plastic needle cap attached to the dental syringe containing an empty cartridge was pushed against, but did not penetrate, the intraoral soft tissue at the site of the previous LA injection. This sham allowed for a blinded comparison of injection site pain. After receiving PM or the sham injection, all patients were observed for 5 hours to collect efficacy and safety data, and then monitored for up to 48 hours.

The 5-hour observation and testing period was a primary determinant in the lower age limit (4 years) for patients. It was felt (correctly, it turned out) that younger patients would be unable to cooperate fully with the assessments required over the 5-hour period of observation.

Lip and Tongue Palpation: All patients were trained in assessing the numbness of their lips. Those in the mandibular protocol were also trained to tap their tongues. The procedure involved a light tapping of these soft tissues with their index or middle finger. The research assistants instructed patients that during the study they would rate the injected side as either feeling normal, tingling, or numb, and that they may tap the noninjected side as a comparison. Assessments were made every 5 minutes.

STAR Questionnaire: The STAR Questionnaire measures quality of life (Table 3). It was developed specifically for these studies to quantify a patient's perceived clinical benefit from reversing STA.

Functional Assessment Battery (FAB): The FAB included measurements of smiling, speaking, and drooling, and drinking 3 ounces of water at various time points during the study. Each functional assessment was rated as normal or abnormal by a research assistant and the patient.

Heft-Parker Visual Analogue Scale (H-P VAS): The H-P VAS is a 170 mm visual analog scale containing the following verbal descriptors: none, faint, weak, mild,
moderate, strong, intense, and maximum possible. Patients were asked to place a mark on the line that corresponded to their current assessment of pain at the injection site and the procedural site.

**Efficacy of PM: Adolescents and Adults**

In the maxillary trial, the median time to recovery of normal sensation in the upper lip was 50 minutes for PM patients and 132.5 minutes for sham patients, a reduction in upper lip anesthesia of 82.5 minutes \((P < .0001)\).

In the mandibular trial, the median time to recovery of normal sensation in the lower lip was 70 minutes for PM patients and 155 minutes for sham patients, a reduction in lower lip anesthesia of 85 minutes \((P < .0001)\).

Interestingly, within 30 minutes of PM administration, 26.7% of maxillary patients reported return of normal lip sensation as compared with 1.7% in the control group. At one hour 59.2% had normal upper lip sensation versus 11.7% for sham. At 90 minutes these figures were 75% and 25%, respectively. Upper lip anesthesia persisting beyond 2 hours occurred in 54.2% of sham patients versus 11.6% of PM patients (Figure 5).

In the mandible, within 30 minutes of PM administration, 17.2% of patients reported normal lower lip sensation as compared with 0.8% in the control group. At one hour 41% had normal lower lip sensation versus 7.4% for sham. At 90 minutes these figures were 70.5% and 13.1%, respectively. Lower lip anesthesia persisting beyond 2 hours occurred in 70.5% of sham patients versus 18.9% in PM patients (Figure 6).

The median time to return of normal sensation to the tongue was 60 minutes for PM and 125 minutes for sham-treated patients, a statistically significant \((P < .0001)\) difference of 65 minutes.

**Safety of PM: Adolescents and Adults**

The overall frequency and the nature of adverse events (AEs) reported in both the maxillary and mandibular studies appeared similar in nature and frequency. In the maxillary study, a total of 38 patients reported 50 AEs; 32 AEs in 22 patients in the PM group; 18 AEs in 16 patients in the sham group. In the mandibular study, a total of 63 patients reported 77 AEs; 44 AEs in 34 patients in the PM group; 33 AEs in 29
patients in the sham group. None of the AEs in either study were serious or rated severe, and no patient was discontinued from the study because of an AE.

Dental patients were administered a dose of either 0.2, 0.4 or 0.8 mg of PM. Table 4 lists adverse reactions in which the frequency was greater than or equal to 3% in any PM dose group and was equal to or exceeded that of the control group. These included diarrhea, facial swelling, increased blood pressure/hypertension, injection site reactions, jaw pain, oral pain, paresthesia, pruritis, tenderness, upper abdominal pain, and vomiting. The majority of adverse reactions were mild and resolved within 48 hours.22

Safety and Efficacy of PM: Children18
In a Phase II, double-blinded, randomized, multicenter (n = 11), controlled study, pediatric patients between the ages of 4 and 11 years received 2% lidocaine + epinephrine 1:100,000 and either PM or sham injection. One hundred fifty-two patients were enrolled and completed the study. There were 96 in the PM group and 56 in the sham injection group. Patients received one half cartridge of LA if they weighed >15 kg but <30 kg, and 1/2 or a full cartridge if they weighed ≥ 30 kg. Median time to normal lip sensation was evaluated in patients 6 to 11 years of age who were trainable for lip palpation procedures (see above). The reduction in median time to normal lip sensation for PM patients (n = 60) was 60 minutes compared to 135 minutes in the sham group (n = 43), representing a reduction of residual STA of 75 minutes (55.6%) for both maxillary and mandibular. Within one hour following administration of PM, 61% of patients reported normal lip sensation, while only 21% of patients in the sham injection group reported normal lip sensation. The finding was statistically significant (P < .0001).

Thirty-five of the 152 patients (23%) reported 37 adverse events with similar frequencies in both PM (20.8%) and sham (26.8%) groups. There were no deaths or other serious AEs, and all patients completed the study. All but 3 AEs were mild or moderate in severity. One patient in the PM and 2 in the sham group reported severe AEs: postdental procedure pain (PM, sham) and injection site pain (sham). All AEs were transient and resolved within the study period.

Clinical Indications for Reversal of LA
Administration of OraVerse should be a treatment option whenever prolonged STA presents a potential risk (soft-tissue injury) or will negatively impact the patient's lifestyle (ie, inability to speak or eat). Table 5 lists potential candidates for reversal of STA.

A situation which does not usually represent indications for STA reversal includes post-surgical patients, where prolonged STA is welcomed as a means of preventing

### Table 4. Adverse Reactions with Frequency ≥ 3% and Equal to or Exceeding Control

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>OraVerse</th>
<th>Total</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2 mg</td>
<td>0.4 mg</td>
<td>0.8 mg</td>
</tr>
<tr>
<td></td>
<td>(N = 83)</td>
<td>(N = 284)</td>
<td>(N = 51)</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>15 (18)</td>
<td>82 (29)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0 (0)</td>
<td>17 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>5 (6)</td>
<td>15 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Post procedural pain</td>
<td>3 (4)</td>
<td>17 (6)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>10 (4)</td>
<td>3 (6)</td>
</tr>
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break-through pain. Further, following LA administration via the PDL, also known as ILI or intraosseous injection, the localized area of STA associated with these injections precludes the use of PM.

**Clinical Use of PM in Dentistry**

OraVerse (phentolamine mesylate) is indicated for the reversal of STA, ie, anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a LA containing a vasoconstrictor. OraVerse is not recommended for use in children under 6 years of age or weighing less than 15 kg (33 lbs).22

The recommended dose of OraVerse is based on the number of cartridges of LA + vasoconstrictor administered. It is administered in an equal volume, up to a maximum of 2 cartridges (Table 6).

OraVerse is administered at the same location(s) and by the same technique(s) (nerve block or infiltration) used earlier for the LA administration.22

Adverse reactions associated with the administration of PM have been discussed earlier (safety and adverse reaction discussion). Other potential complications are trismus and paresthesia, both of which are related to the act of injection rather than to the drug itself.

### SUMMARY

PM (OraVerse) enables the dentist or dental hygienist (where permitted) to significantly decrease the duration of residual STA in patients where such numbness may prove to be potentially injurious (children, geriatric, and special needs patients), or a negative influence on their quality of life (speaking, eating, negative body image). (Note: As of August 3, 2009, dental hygienists are permitted to administer PM in the following states: Alaska, Arkansas, Hawaii, Idaho, Iowa, Louisiana, Montana, Nevada, New York, North Dakota, Oklahoma, Rhode Island, Tennessee, Utah, and Wisconsin.)

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### Table 5. Potential Treatments/Candidates for Reversal of Residual STA

<table>
<thead>
<tr>
<th>Conservative dental treatment</th>
<th>Nonsurgical periodontics (eg root planing and curettage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric patients</td>
<td>Geriatric patients</td>
</tr>
<tr>
<td>Special needs patients</td>
<td>Medically compromised patients (eg, diabetics)</td>
</tr>
</tbody>
</table>

### Table 6. Dosing and Administration of OraVerse

<table>
<thead>
<tr>
<th>Volume of local anesthetic Administered (cartridges)</th>
<th>Dose of OraVerse in cartridges (mg PM)</th>
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<td>1</td>
<td>1 (0.4 mg)</td>
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<td>2</td>
<td>2 (0.8 mg)</td>
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REFERENCES


POST EXAMINATION INFORMATION

To receive continuing education credit for participation in this educational activity you must complete the program post examination and receive a score of 70% or better.

Traditional Completion Option:
You may fax or mail your answers with payment to Dentistry Today (see Traditional Completion Information on following page). All information requested must be provided in order to process the program for credit. Be sure to complete your “Payment,” “Personal Certification Information,” “Answers,” and “Evaluation” forms. Your exam will be graded within 72 hours of receipt. Upon successful completion of the post-exam (70% or higher), a letter of completion will be mailed to the address provided.

Online Completion Option:
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General Program Information:
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POST EXAMINATION QUESTIONS

1. Which one of the following local anesthetic (LA) combinations provides the longest duration of pulpal and soft tissue anesthesia (STA)?
   a. Articaine 4% + epinephrine 1:100,000.
   b. Bupivacaine 0.5% + epinephrine 1:200,000.
   c. Lidocaine 2% + epinephrine 1:100,000.
   d. Mepivacaine 3%.

2. Which of the following techniques provides successful mandibular pulpal anesthesia in the adult without also producing STA of the tongue or lip?
   a. Gow-Gates mandibular nerve block.
   b. Periodontal ligament injection.
   c. Inferior alveolar nerve block.
   d. Mandibular infiltration.

3. Traumatic injury to the lower lip occurred in approximately what percentage of children between the ages of 4 and 7 years following inferior alveolar nerve block (IANB)?
   a. 45%.
   b. 16%.
   c. 9%.
   d. 1%.

4. LAs prevent pain by:
   a. Preventing the pain impulse from reaching the brain.
   b. Modifying the patient’s response to the pain impulse once it reaches the brain.
   c. Preventing the pain impulse from ever being created.
   d. None of the above.

5. A 1980s attempt to reverse the residual STA associated with LAs was:
   a. Acupuncture.
   b. Hypnosis.
   c. Iontophoresis.
   d. Transcutaneous electrical nerve stimulation.

6. Phentolamine is approved by the US Food and Drug Administration (FDA) for all of the following except:
   a. Diagnosis of pheochromocytoma.
   b. Prevention of soft-tissue necrosis following accidental catecholamine extravasation.
   c. Bronchodilation.
   d. Treatment of hypertensive crisis.
7. Phentolamine is classified as a Pregnancy Class ____ drug by the FDA?
   a. A
   b. B
   c. C
   d. X

8. FDA mandated clinical drug trials Phase ____ studies utilizing between 20 and 300 patients are designed to assess the drug's efficacy as well as further assess safety.
   a. Phase I.
   b. Phase II.
   c. Phase III.
   d. Phase IV.

9. The ________ was designed to measure a patient's quality of life following LA injection.
   a. STAR questionnaire.
   b. Functional assessment battery.
   c. Stevenson-Malamed Sliding Scale.
   d. Heft-Parker Visual Analogue Scale.

10. The form of phentolamine mesylate (PM) used to reverse LA is approximately ________ the concentration of the medical form of the drug.
    a. The medical and dental forms are equal in concentration.
    b. One fifth.
    c. One tenth.
    d. One twentieth.

11. Within 60 minutes of PM injection ____ of patients had full recovery of sensation in the lower lip.
    a. 5%.
    b. 17%.
    c. 41%.
    d. 83%.

12. ____% of patients still had residual STA of the upper lip lasting more than 2 hours following sham injection.
    a. 9%.
    b. 87%.
    c. 21%.
    d. 54%.

13. Which of the following statements regarding adverse events (AEs) associated with PM administration is TRUE?
    a. Patients receiving PM reported twice the number of AEs as the controls.
    b. Patients receiving PM had significantly fewer AEs than the controls.
    c. Bradycardia and tachycardia occurred significantly more often in patients than in the controls.
    d. The incidence, and type, of AEs reported were similar in both PM and control groups.

14. In which of the following dental treatments would reversal of residual STA usually NOT be desirable?
    a. Surgical extraction of third molars.
    b. Root planing and curettage.
    c. MOD onlay of tooth No.12.
    d. Seven-year-old following IANB.

15. In which of the following situations would residual STA reversal NOT be indicated (having received a LA containing a vasoconstrictor)?
    a. A 3-year-old patient following restorations on 3 mandibular teeth.
    b. Type 1 diabetic following IANB.
    c. An 85-year-old patient with mild dementia, following IANB.
    d. None of the above.

16. Following 3.6 mL of lidocaine hydrogen chloride + epinephrine 1:100,000 via IANB, the suggested volume of PM for residual STA reversal is?
    a. 0.9 mL.
    b. 1.8 mL.
    c. 2.7 mL.
    d. 3.6 mL.
PROGRAM COMPLETION INFORMATION

If you wish to purchase and complete this activity traditionally (mail or fax) rather than online, you must provide the information requested below. Please be sure to select your answers carefully and complete the evaluation information. To receive credit you must answer at least 12 of the 16 questions correctly.

Complete online at: dentalce.today.com

TRADITIONAL COMPLETION INFORMATION:

Mail or Fax this completed form with payment to:

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Fairfield, NJ 07004
Fax: 973-882-3622

PAYMENT & CREDIT INFORMATION:

Examination Fee: $40.00  Credit Hours: 2.0

Note: There is a $10 surcharge to process a check drawn on any bank other than a US bank. Should you have additional questions, please contact us at (973) 882-4700.

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My Credit Card information is provided below.

☐ American Express  ☐ Visa  ☐ MC  ☐ Discover

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Suite or Apartment Number

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Daytime Telephone Number With Area Code

Fax Number With Area Code

E-mail Address

ANSWER FORM: COURSE #: 123

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

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Please complete the following activity evaluation questions.

Rating Scale: Excellent = 5 and Poor = 0

Course objectives were achieved. __________

Content was useful and benefited your clinical practice. __________

Review questions were clear and relevant to the editorial. __________

Illustrations and photographs were clear and relevant. __________

Written presentation was informative and concise. __________

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