Phentolamine mesylate for the reversal of residual soft-tissue anesthesia

A Peer-Reviewed Publication
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Educational Objectives
The overall goal of this article is to provide information on the accelerated reversal of the associated residual soft-tissue numbness following dental procedures.

Upon completion of this course, the clinician will be able to do the following:
1. List and describe the types of local anesthetics that were introduced to dentistry over time
2. Describe the time for which residual soft-tissue anesthesia can persist and patient perceptions of this
3. List and describe the safety and efficacy of phentolamine mesylate based on clinical data presented
4. List the age groups for which phentolamine mesylate can be used for the reversal of soft-tissue anesthesia, applicable dosing, and describe potential side effects.

Abstract
The most frequently administered drugs in dentistry are local anesthetics. These provide relief from pain during procedures, leaving inconvenient residual numbness that takes some time to wear off following completion of dental procedures. Recently, a new drug has been approved for acceleration of the reversal of soft-tissue local anesthesia in patients age 6 and older. This new drug adds a new dimension to the pain management armamentarium of dentists.

Introduction
Local anesthetics are the most administered drugs in dentistry. Local anesthetics also represent the safest and the most effective drugs available in medicine for both the control and prevention of pain occurring during and following invasive procedures. In the United States, more than 300 million dental local anesthetic cartridges are sold annually. Given that multiple injections (in the same patient) are often administered with each cartridge, it is conservatively estimated that more than 500 million local anesthetic injections are administered by US dentists each year.

Cocaine, the first local anesthetic, was injected along with epinephrine via inferior alveolar nerve block in 1884 to a patient by the famed American surgeon William Stewart Halsted (1852–1922). Though effective, it was soon evident that cocaine possessed significant side effects, not the least of which was addiction (which severely afflicted Halsted). In 1905, the first amino-ester anesthetic, procaine, was synthesized in Germany and marketed as Novocain, a name that has become synonymous with dental anesthesia throughout the world. Other ester-type local anesthetics followed, including butacaine, chloroprocaine, piperocaine, propoxycaíne, and tetracaine. Administered as a 2% solution with epinephrine 1:100,000, procaine provided short-duration pulpal and soft-tissue anesthesia (STA) that was adequate for the overwhelming majority of dental procedures performed during the early 1900s. Three factors arose that led, in the 1940s, to the search for newer, more effective local anesthetics. First, and most significant, was the increasing allergenicity of procaine and the other ester-type local anesthetics. After 40 years of exposure, a significant number of persons had become sensitized to the ester-type local anesthetics. Additionally, the exceedingly slow onset of clinical anesthesia following administration of procaine was irksome to increasing numbers of dentists; procaine 2% has an onset of anesthesia ranging from 6 to 10 minutes. A third factor leading to the search for newer, more effective local anesthetics was the short duration of both pulpal and soft-tissue anesthesia. Dentistry was changing, with procedures of longer duration undertaken. Procaine was no longer viewed as the ideal anesthetic drug.

In 1943, in Sweden, Nils Lofgren synthesized lidocaine. This was the first amino-amide local anesthetic. With a more rapid onset, longer duration, and greater efficacy, lidocaine (under the proprietary name Xylocaine) soon replaced procaine as the most used local anesthetic in dentistry and medicine. Available as a 2% formulation with epinephrine 1:50,000 and 1:100,000, it provided approximately 1 hour of pulpal and 3 to 5 hours of soft-tissue anesthesia. Lidocaine’s popularity led to the introduction of other amino-amide local anesthetics such as mepivacaine (1960) and prilocaine (1965). With the addition of a vasoconstrictor, these drugs usually provide pulpal anesthesia that lasts approximately 1 hour. As the typical nonsurgical dental procedure lasts approximately 47 minutes, these local anesthetics represent the most-used drugs in dentistry. In 1969, a new local anesthetic, articaine, was synthesized. With the generic name changed to articaine, it was introduced as Ultracaine in Germany in 1976 and as Septocaine in the United States in 2000. The articaine molecule is actually a hybrid of the amino-ester and amino-amide drugs. Similar in action to the other amides, articaine provides approximately 1 hour of pulpal and 3 to 5 hours of STA.

As surgical procedures, including dental implants, became increasingly common, the requirement for longer-acting local an-
esthetics grew. Two drugs, bupivacaine and etidocaine, were introduced into the dental market in 1979 and 1984, respectively. Able to provide STA for periods of up to 12 hours, these drugs are commonly employed for postsurgical pain control. In 2002, etidocaine was withdrawn from the North American dental market.

Figure 2. Procaine (ester), lidocaine (amide) and articaine

<table>
<thead>
<tr>
<th>Procaine</th>
<th>Lidocaine</th>
<th>Articaine</th>
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<tbody>
<tr>
<td><img src="image1" alt="Procaine" /></td>
<td><img src="image2" alt="Lidocaine" /></td>
<td><img src="image3" alt="Articaine" /></td>
</tr>
</tbody>
</table>

**Duration of anesthesia**

Currently, dentists are equipped with a local anesthetic armamentarium consisting of multiple drug combinations that provide durations of pulpal and soft-tissue anesthesia capable of managing the pain control requirements of all dental patients.

Local anesthetics can be categorized based upon the expected duration of pulpal anesthesia: short-, intermediate-, and long-duration. A number of factors act to influence these expected durations, usually in a negative way. Approximately 70% of persons will respond ‘normally’ when administered the ‘average’ dose of a drug. Fifteen percent will exhibit longer durations than those listed (hyperresponders), while the remaining 15% demonstrate shorter durations (hyporesponders). Other factors affecting expected durations of anesthesia include technique (accuracy), status of the tissue at the site of LA deposition, anatomical variation, the type of injection (infiltration vs. nerve block) and chronobiology (time of day).

For all local anesthetic formulations in all duration categories, the duration of STA greatly exceeds that of pulpal anesthesia. For the long-duration category, this is an important reason for using bupivacaine. The primary indication for bupivacaine + epinephrine is for the prevention of pain in the postsurgical period. Administered by nerve block at the conclusion of a surgical procedure, the drug, which is commonly used in conjunction with orally administered nonsteroidal anti-inflammatory drugs, can make the postsurgical period comfortable (i.e., painless) for the vast majority of patients. However, most dental treatments do not require pain management once the patient is discharged from the office. Pulpal anesthesia has provided for pain-free dental care during treatment, but upon discharge from the dental office, the patient is faced with a period of residual soft-tissue anesthesia that may range from an additional 1–2 hours (3% mepivacaine) up to as many as 5–6 hours (articaine, lidocaine, mepivacaine, and prilocaine with vasoconstrictor).

**Residual soft-tissue anesthesia**

Residual soft-tissue anesthesia (STA), though beneficial following many surgical interventions, can also prove to be detrimental. Without sensation in their lips and/or tongues, patients may accidentally chew or bite the soft tissues, inflicting potentially significant traumatic injury (Figures 3 and 4). As always, the doctor must weigh the benefit to be gained from the postsurgical administration of a drug such as bupivacaine for pain prevention versus the potential risk of self-inflicted soft-tissue injury. The patient’s desires should be a part of this decision.

Most dental procedures, on the other hand, are of relatively short duration, lasting, on an average, 47 minutes. Procedures such as routine restorations and scaling and root planing are typically completed in less than one hour and are rarely associated with a need for post-operative pain control. However, the need for effective intraoperative pain control normally mandates the use of a local anesthetic containing a vasoconstrictor, such as epinephrine or levonorgestrel, and has become a routine part of dentistry. Patients commonly are discharged from the dental office with residual numbness to their lips and tongue typically persisting for 3 to 5 hours.

Figure 3. Traumatic injury in a patient, associated with lack of sensation


Figure 4. Traumatic injury in a second patient

Traumatic soft-tissue injury can occur in any patient. However, it is in pediatric and mentally disabled adult patients where self-inflicted injury is more apt to commonly be seen. A survey of pediatric patients by College et al. revealed that 13% of inferior alveolar nerve blocks were associated with inadvertent biting of the lips. By age group, trauma frequency was 18% (< 4 years), 16% (4–7 years), 13% (8–11 years) and 7% (> 12 years). Though infrequent, such injury does occur in the adult population as well.

Most commonly, residual STA represents an inconvenience and/or embarrassment to the patient who, upon leaving the dental office, wishes only to return to his or her normal life. Patients feel that residual STA interferes with their normal daily activities in three areas: perceptual (perception of altered physical appearance), sensory (lack of sensation), and functional (diminished ability to speak, smile, drink, and control drooling). For many patients, this becomes a significant detriment to their quality of life, as made famous in the comedy routines of Mr. Bill Cosby and Mr. Dudley Moore. Patients may complain to their doctors at subsequent appointments that they were unable to eat a meal or to talk normally for many hours after their last dental visit because their lips and/or tongue were still numb. The request of “Doctor, can’t you make the numbness go away faster?” has been uttered by many patients to most doctors.

Reversal of residual soft-tissue anesthesis

Efforts at eliminating or minimizing the duration of residual STA were made over the years with a uniform lack of success. One of the more promising techniques employed was the utilization intraorally of the medical procedure known as transcutaneous electrical nerve stimulation (TENS). TENS has been employed in medicine for a great many years and involves the delivery of a low-frequency electrical stimulus to an area to provide pain relief for chronic pain as well as relief of edema. When used for chronic pain management, low-frequency stimulation provokes the release of serotonin, beta-endorphins, and enkephalins, thereby acting to raise the pain reaction threshold. In sports medicine, the application of a low-frequency electrical current to an area that has been injured recently can be of benefit to the patient: It acts to increase tissue perfusion produced by capillary and arteriolar dilation while stimulating the contraction of skeletal muscles. The net effect of these two processes is to provide a pumping action in the area of application of the current. Therapeutically, a 1-hour treatment at a low frequency (2.5 Hz) helps to decrease edema (skeletal muscle-stimulating effect), and the increased perfusion and skeletal muscle stimulation act together to “cleanse” the area of tissue-injury breakdown products. The use of TENS in this manner speeds the recovery process, enabling the athlete to return to the playing field sooner.

It is in this second use of TENS that the concept of reversing local anesthesia was born (Figure 5). Applying intraoral electrodes at low-frequency stimulation causes a muscle contraction that produces a pumping action similar to that employed for the reduction of edema in sports medicine. Muscle contraction would pump the ‘fluid’ (i.e., local anesthetic) out of the site and into the cardiovascular system, effectively diminishing the duration of STA. Though somewhat successful, the use of intraoral TENS (termed EDA or electronic dental anesthesia) never became popular, due primarily to the cumbersome apparatus required for its intraoral use and the limited success achieved when used to manage the acute pain associated with restorative dental procedures.

Techniques of local anesthetic administration – such as the periodontal ligament injection PDL, intraligamentary (IL) injection, intraosseous (IO) anesthesia, the anterior middle superior alveolar (AMSA) injection, and computer-controlled local anesthetic delivery systems – have provided the means, in limited situations, of administering clinically adequate pain control with little or no extraoral soft-tissue anesthesia. Until the advent of phentolamine mesylate, no therapeutic modality existed to hasten the return of normal sensation and function after local anesthetic injection.

Phentolamine mesylate

Phentolamine mesylate (Figure 6) is a nonselective alpha-adrenergic-blocking agent that has been on the market in the United States since 1952. It has been FDA approved as an intravenous/intramuscular formulation indicated for the treatment of dermal necrosis resulting from the extravasation of the vasoconstrictors norepinephrine and epinephrine and for the diagnosis and treatment of severe hypertension in patients with pheochromocytoma, a rare tumor of the adrenal medulla that secretes excessive epinephrine and norepinephrine. Phentolamine (Regitine) is also used for the management of catecholamine-induced hypertensive crises (e.g., pheochromocytoma, MAOI crisis, cocaine overdose). Phentolamine is usually given intravenously in 1-to-5-mg boluses, although it may be given as an infusion at a rate of 5 to 10 μg/kg/min. The effect is immediate and may last up to 15 minutes. Reflex tachycardia may be seen.
Clinical effects of phentolamine include peripheral vasodilation and tachycardia. Vasodilation is a result of both direct relaxation of vascular smooth muscle and alpha blockage. The drug produces positive inotropic and chronotropic effects, leading to increased 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. Following the administration of a local anesthetic with a vasoconstrictor, a subsequent phentolamine injection into the same location could theoretically enhance redistribution of the local anesthetic away from the injection site, providing a more rapid return of normal intraoral and perioral sensation.

Phentolamine mesylate for the reversal of residual soft-tissue anesthesia

Clinical Trials

An injectable form of phentolamine mesylate has been developed for the acceleration of the reversal of residual soft-tissue anesthesia (once the numbing action of local anesthesia is no longer desirable). In May 2008, the FDA granted approval of OraVerse™ (phentolamine mesylate) Injection for the reversal of soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. OraVerse is recommended for use in dental patients 6 years or older, or weighing at least 15 kg. The product contains 0.4 mg phentolamine mesylate (0.235 mg/ml) packaged in a standard 1.8 ml dental cartridge.

Prior to receiving FDA approval, a number of clinical trials were conducted to demonstrate the safety and efficacy of phentolamine mesylate for this new therapeutic indication. Two phase 3, double-blinded, randomized, multicenter controlled studies in adult patients age 12 and older were undertaken. One trial investigated the effectiveness of OraVerse in mandibular soft-tissue anesthesia reversal, while the second investigated the effectiveness of OraVerse in reversing maxillary STA. In addition, a pediatric phase 2, double-blinded, randomized, multicenter controlled study was conducted in dental patients age 4 to 11 years who had received 2% lidocaine with 1:100,000 epinephrine.

Phase 3 Clinical Trials – Adolescents and Adults

In the phase 3 trials, patients 12 years and older received a local anesthetic containing a vasoconstrictor on one side of their mouth prior to a restorative or periodontal maintenance procedure. Eighteen research centers were involved in the mandibular trial, sixteen in the maxillary trial. The primary end point was the time required for lip sensation to return to normal, as measured by the patients. Additional end points included patients’ perception of altered function, sensation, and appearance, and their actual function (smiling, speaking, drinking, and drooling), as assessed by both the patient and a blinded observer. In the mandibular study, the time to recovery of tongue sensation was a secondary end point.

The dental procedure had to be completed within 60 minutes of the local anesthetic injection, and the patient’s lip had to still be numb at that time, otherwise he or she was excluded from the study. All 244 patients randomized in the mandibular study reported lip anesthesia at 1 hour (or at the end of the procedure), while 194 patients reported that their tongues were also numb at this time. The maxillary study enrolled 240 patients. Patients were first randomized to receive 1 of 4 local anesthetics (i.e., 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) in a 6:1:1:1 ratio based on usage patterns in the United States.

At the conclusion of the dental procedure, patients were randomized to receive either OraVerse or a control in a 1:1 ratio. Both the patient and the investigator were blinded to the treatment assigned. OraVerse was administered at the same injection site(s) using the same administration method as the previous local anesthetic injection(s), with patients receiving a dose of 0.4 mg or 0.8 mg of phentolamine mesylate. 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 local anesthetic injection, allowing for a blinded comparison of injection site pain. After receiving the OraVerse or sham injection, patients were observed for 5 hours to collect efficacy and safety data, and then monitored for up to 48 hours.

Study Assessments – Efficacy

Lip and Tongue Palpation: All patients were trained in assessing the numbness of their lips using a standardized palpation procedure. Those in the mandibular protocol were also trained to assess their tongue. The procedure involved a light tapping of these soft tissues with the 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 could tap the noninjected side as a comparison. Assessments were performed every 5 minutes.

STAR Questionnaire: The STAR (soft-tissue anesthesia recovery) questionnaire measured the patient’s perception of altered function, sensation, and appearance and perceived clinical benefit from reversing soft-tissue anesthesia. It was developed specifically for these studies. Assessments were performed every 30 minutes.

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

Efficacy Results

Maxillary Trial

In the maxillary trial, the median time to recovery of normal sensation in the upper lip was 50 minutes for OraVerse patients and 132.5 minutes for sham patients, representing a
reduction in upper lip anesthesia of 82.5 minutes. This result was statistically significant (p <0.0001).30

Interestingly, within 30 minutes of OraVerse administration, 26.7% of patients reported normal lip sensation as compared with 1.7% in the control group in the upper lip. At 1 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 90 minutes occurred in 75% of sham patients versus 25% of OraVerse patients (Table 1).

Mandibular Trial
In the mandibular trial, the median time to recovery of normal sensation in the lower lip was 70 minutes for OraVerse patients and 155 minutes for sham patients, representing a reduction in lower lip anesthesia of 85 minutes. The difference between these times was statistically significant (p <0.0001).30 Within 30 minutes of OraVerse administration, 17.2% of patients reported normal lower lip sensation as compared with 0.8% in the control group. At 1 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 90 minutes occurred in 86.9% of sham patients versus 29.5% of OraVerse patients. The median time for return of normal sensation to the tongue was 60 minutes for OraVerse and 125 minutes for sham-treated patients, a statistically significant (p <0.0001) difference of 65 minutes.30

| Table 1. Phentolamine mesylate vs. sham injection. Return of normal sensation
<table>
<thead>
<tr>
<th>Maxillary arch</th>
<th>Mandibular arch</th>
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<tbody>
<tr>
<td>OraVerse</td>
<td>Sham</td>
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<tr>
<td><strong>Percentage with normal lip sensation</strong></td>
<td></td>
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<tr>
<td>After 30 minutes</td>
<td>26.70%</td>
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<tr>
<td>After 60 minutes</td>
<td>59.20%</td>
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<tr>
<td>After 90 minutes</td>
<td>75%</td>
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<tr>
<td><strong>Median time to recovery (in minutes)</strong></td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>50</td>
</tr>
<tr>
<td>Tongue</td>
<td>60</td>
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</table>

Safety Results:
The overall frequency and the nature of AEs reported in both the maxillary and mandibular studies appeared similar in nature and frequency in individuals randomly assigned to each treatment group. In the maxillary study, a total of 38 patients reported 50 treatment-emergent AEs: in the OraVerse group, 22 patients reported 32 AEs, and 16 patients reported 18 AEs in the sham group. Blinded researchers judged 25 AEs in the OraVerse group and 14 AEs in the sham group to be related to the study drug injection. In the mandibular study, a total of 63 patients reported 77 treatment-emergent AEs: 44 AEs in 34 patients in the OraVerse group, and 33 AEs in 29 patients in the sham group. Blinded researchers judged 32 AEs in the OraVerse group and 23 AEs in the sham group to be related to the study drug injection. None of the AEs in either study were serious or rated severe, and no patient was discontinued from the study because of an AE.30

The majority of patients in both OraVerse and sham groups experienced no pain or mild oral pain, with less than 10% of patients in each group reporting moderate oral pain. Mean H-P VAS pain scores associated with either patient group corresponded to faint pain only. No patients experienced severe pain.

No differences were found in oral cavity assessments and vital sign measurements between the OraVerse and the sham groups.

**Phase 2 Clinical Trial – Pediatrics**
In the phase 2, double-blinded, randomized, multicenter (n = 11) controlled study, pediatric patients between the ages of 4 and 11 received 2% lidocaine + epinephrine 1:100,000 and either OraVerse or sham injection.31 One-hundred and fifty-two patients were enrolled and randomized to OraVerse and sham injections in a 2:1 ratio, and then completed the study. There were 96 patients in the OraVerse group and 56 in the sham group. Patients received half a cartridge of local anesthetic if they weighed at least 15 and less than 30 kg, and half or a full cartridge if they weighed 30 kg or more. Median time to normal lip and tongue sensation was evaluated.

The reduction in median time to normal lip sensation for OraVerse patients (n=72) 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 arches. Within 1 hour following administration of OraVerse, 61% of patients reported normal lip sensation, while only 21% of patients in the sham group reported normal lip sensation. This finding was statistically significant (p <0.0001). The reduction in median time to normal tongue sensation for OraVerse patients (n=32) was 45 minutes, compared to 112.5 minutes in the sham group (n=16), representing a statistically significant reduction of residual STA of 67.5 minutes (60.0%).

Thirty-five of the 152 patients (23%) reported 37 treatment-emergent AEs with similar frequencies in both OraVerse (20.8%) and sham (26.8%) groups. Of these 37 AEs, 16 (16.6%) were judged to be related to treatment in the OraVerse group, with 7 (12.5%) related to the sham group. There were no serious AEs, and all patients completed the study. All but 3 AEs were mild or...
moderate in severity. One patient in the OraVerse and 2 in the sham group reported severe AEs: post-dental-procedure pain (OraVerse, sham) and injection site pain (sham). All AEs were transient and resolved within the study period. OraVerse had no measurable effect on the frequencies of AEs, vital signs, intraoral pain, or clinically significant soft-tissue changes.

**Prescribing Information for OraVerse™**

OraVerse is marketed in 1.8 ml cartridges containing 0.4 mg. phentolamine mesylate in a 1.7 ml solution. It is indicated for the reversal of soft-tissue anesthesia, i.e. anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor, and is administered using the same location(s) and same technique(s) (infiltration or block injection) used for the administration of L.A.

The maximum recommended dose for adult patients is 2 cartridges. OraVerse is not recommended for use in children less than 6 years of age or weighing less than 15 kg (33 lbs). In pediatric patients weighing between 15 and less than 30 kg the maximum dose of OraVerse recommended is 3 cartridges (0.8 mg phentolamine mesylate). In pediatric patients weighing between 15 and less than 15 kg (33 lbs) the maximum dose of OraVerse recommended is (33 lbs). All AEs were transient and resolved within the study period. OraVerse had no measurable effect on the frequencies of AEs, vital signs, intraoral pain, or clinically significant soft-tissue changes.

<table>
<thead>
<tr>
<th>Amount of Local Anesthetic Administered</th>
<th>Dose (mg phentolamine mesylate)</th>
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<tr>
<td>½ Cartridge</td>
<td>½ Cartridge (0.2 mg)</td>
</tr>
<tr>
<td>1 Cartridge</td>
<td>1 Cartridge (0.4 mg)</td>
</tr>
<tr>
<td>2 Cartridges</td>
<td>2 Cartridges (0.8 mg)</td>
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**Table 2: Dosing and Administration**

OraVerse should be administered following the dental procedure using the same location(s) and technique(s) (infiltration or nerve block injection) employed for the administration of the local anesthetic.

In dental patients administered a dose of ½, 1 or 2 cartridges of OraVerse, the majority of adverse reactions were mild and resolved within 48 hours. Table 3 lists adverse reactions in which the frequency of AEs was greater than or equal to 3% in any OraVerse dose group and was equal to or exceeded that of the control group.

**Candidates for local anesthesia reversal**

A majority of dental treatments today are not so traumatic in nature that they require a patient to leave the dental office with residual STA that commonly persists for many hours while gradually resolving. These include conservative dental restorations, crowns, and periodontal maintenance procedures such as scaling and root planing. In addition, pediatric patients, whether in the general dentistry or pediatric dentistry office, will benefit from the diminished soft-tissue duration associated with phentolamine mesylate administration. Patients with medical conditions requiring strict adherence to eating regimens, such as diabetics, will also benefit from the reversed soft-tissue nature that they require a patient to leave the dental office with residual STA that commonly persists for many hours while gradually resolving. These include conservative dental restorations, crowns, and periodontal maintenance procedures such as scaling and root planing. In addition, pediatric patients, whether in the general dentistry or pediatric dentistry office, will benefit from the diminished soft-tissue duration associated with phentolamine mesylate administration. Patients with medical conditions requiring strict adherence to eating regimens, such as diabetics, will also benefit from the reversal of anesthesia.

**Summary**

Phentolamine mesylate adds a new dimension to the pain management armamentarium of dentists. Not only do we possess an array of local anesthetics capable of providing clinical pain control for essentially all dental procedures, including postsurgical pain management, with phentolamine mesylate we now possess the ability to more quickly remove the oftentimes bothersome specter of prolonged soft-tissue anesthesia.
Glossary of Terms

Alpha-adrenergic blocking agents: These are a group of drugs that selectively inhibit the activities of alpha receptors in the sympathetic nervous system. As with beta-blocking agents, alpha-adrenergic blocking agents compete with the catecholamines at peripheral autonomic receptor sites.

Phase-1 trials: These are the first stage of testing in human subjects. Normally, a small (20–80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacocoefficacy), 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.

Phase-2 trials: Once the initial safety of the study drug has been confirmed in phase-1 trials, phase-2 trials are performed on larger groups (20–300) and are designed to assess how well the drug works, as well as to continue phase-1 safety assessments in a larger group of volunteers and patients.

Phase-3 trials: These are randomized, controlled multicenter trials on large patient groups (300–3,000 or more, depending upon the disease/medical condition studied) and are aimed at identifying whether the drug is in comparison with current ‘gold standard’ treatment.

References


Author Profile

Dr. Malamed graduated from New York University College of Dentistry in 1969, and completed his residency in anesthesiology at Montefiore Hospital and Medical Center. In 1973, Dr. Malamed joined the faculty of the University of Southern California School of Dentistry in Los Angeles, where he is currently Professor of Anesthesia and Medicine. Dr. Malamed is a diplomate of the American Dental Board of Anesthesiology, and has authored more than 135 scientific papers and 17 chapters in medical and dental journals and textbooks in the areas of physical evaluation, emergency medicine, local anesthesia, sedation, and general anesthesia. In addition, Dr. Malamed is the author of three widely used textbooks, published by CV Mosby Inc: Handbook of Local Anesthesia (5th edition, 2004); Handbook of Medical Emergencies in the Dental Office (6th edition 2007); and Sedation: A Guide to Patient Management (5th edition 2009) as well as two interactive DVDs: Emergency Medicine (2nd edition 2008) and Malamed’s Local Anesthetic Technique (2004).

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Questions

1. It is conservatively estimated that in excess of ________ local anesthetic injections are administered by U.S. dentists each year.
   a. 300 million
   b. 400 million
   c. 500 million
   d. 600 million

2. The first local anesthetic was ________.
   a. lidocaine
   b. cocaine
   c. morphine
   d. bupivacaine

3. The first local anesthetic was injected along with epinephrine via inferior alveolar nerve block in 1884 by the famed American surgeon ________.
   a. Robert McKenzie
   b. Stewart Michael Shoshone
   c. William Stewart Halsted
   d. none of the above

4. ________ was an ester-type local anesthetic that was introduced.
   a. Butivacaine
   b. Procaine
   c. Pipercaine
   d. all of the above

5. ________ was the first amino-amide local anesthetic.
   a. Butivacaine
   b. Lidocaine
   c. Pipercaine
   d. Aminocaine

6. The typical nonsurgical dental procedure lasts approximately ________ minutes.
   a. 27
   b. 37
   c. 47
   d. 57

7. Bupivacaine is able to provide soft-tissue anesthesia for periods of up to ________.
   a. 3 hours
   b. 6 hours
   c. 9 hours
   d. 12 hours

8. Fifteen percent of patients are ________ to local anesthetics.
   a. hypersenders
   b. hyperrespersers
   c. normal responders
   d. a and b

9. The primary indication for bupivacaine + epinephrine is for the prevention of pain in the ________ period.
   a. pre-surgical
   b. surgical
   c. peri-surgical
   d. post-surgical

10. Following a dental procedure, the patient may be faced with a period of residual soft-tissue anesthesia ranging from an additional ________ following use of 3% mepivacaine and up to ________ following use of articaine, lidocaine, mepivacaine, and prilocaine with vasoconstrictor.
    a. 30–45 minutes; 2–3 hours
    b. 1–2 hours; 5–6 hours
    c. none of the above

11. ________ is a factor that can affect the duration of local anesthesia.
    a. Chronology
    b. Status of the tissue at the site
    c. Anatomical variation
    d. all of the above

12. Residual soft-tissue anesthesia results in a temporary lack of sensation in a patient’s lips and/or tongue such that patients ________, inflicting potentially significant traumatic injury.
    a. experience discomfort
    b. may accidentally chew or bite the hard tissues
    c. may accidentally chew or bite the soft tissues
    d. all of the above

13. Procedures such as routine restorations and scaling and root planing are ________ associated with a need for post-operative pain control.
    a. never
    b. rarely
    c. often
    d. always

14. The need for effective intraoperative pain control normally mandates the use of ________.
    a. an anti-inflammatory agent
    b. a topical anesthetic containing a vasoconstrictor
    c. a local anesthetic containing a vasoconstrictor
    d. all of the above

15. Patients commonly are discharged from the dental office with residual numbness of their lips and tongue that typically persists for ________.
    a. 1–2 hours
    b. 2–4 hours
    c. 3–4 hours
    d. 3–5 hours

16. Self-inflicted injury associated with residual soft-tissue anesthesia is apt to commonly be seen in ________.
    a. physically disabled patients
    b. pediatric and geriatric patients
    c. pediatric and mentally disabled adult patients
    d. all of the above

17. Residual soft-tissue anesthesia results in patients experiencing ________.
    a. a perception of altered physical appearance
    b. a lack of sensation
    c. a functional loss
    d. all of the above

18. One of the more promising techniques employed to reverse local anesthesia in the past was ________.
    a. cutaneous electrical nerve modification
    b. subcutaneous electrical nerve stimulation
    c. transcutaneous electrical nerve stimulation
    d. all of the above

19. TENS involves the delivery of a low-frequency electrical stimulus to an area to provide ________.
    a. relief from chronic pain
    b. relief of edema
    c. relief of hyperesthesia
    d. a and b

20. Low-frequency stimulation provokes the release of ________.
    a. serotonin
    b. enkephalins
    c. beta-endorphins
    d. all of the above

21. ________ has provided the means, in limited situations, of administering clinically adequate pain control with little or no extraoral soft-tissue anesthesia.
    a. The periodontal ligament injection
    b. Intranasal anesthesia
    c. The intraligamentary injection
    d. all of the above

22. Phentolamine mesylate is a ________.
    a. nonselective alpha-adrenergic-blocking agent
    b. selective alpha-adrenergic-blocking agent
    c. nonselective beta-adrenergic-blocking agent
    d. none of the above

23. The use of electronic dental anesthesia never became popular, due primarily to the ________.
    a. cumbersome apparatus required
    b. limited success achieved when used to manage the acute pain associated with restorative dental procedures
    c. sensation of pins and needles
    d. a and b

24. ________ is a nonselective alpha-adrenergic-blocking agent.
    a. Lidocaine
    b. Phentolamine mesylate
    c. Morphine
    d. a and b

25. Phentolamine mesylate was FDA approved ________ is a nonselective alpha-adrenergic-blocking agent.
    a. as an intravenous/intramuscular formulation
    b. for the diagnosis and treatment of severe hypertension in patients with pheochromocytoma
    c. for the treatment of dental necrosis resulting from the extravasation of vasoconstrictors
    d. all of the above

26. ________ is used for the management of catecholamine-induced hypertensive crises.
    a. lidocaine
    b. Adrenaline
    c. Morphine
    d. none of the above

27. The vasodilatation seen following administration of phentolamine mesylate is a result of ________.
    a. direct relaxation of vascular smooth muscle
    b. direct relaxation of avascular smooth muscle
    c. alpha blockage
    d. a and c
28. is a clinical effect of phentolamine.
   a. Peripheral vasodilation
   b. Central ataxia
   c. Tachycardia
   d. a and c

29. The FDA granted approval of phentolamine mesylate injection for the reversal of soft-tissue anesthesia in _______.
   a. March 2007
   b. December 2007
   c. May 2008
   d. October 2008

30. Phentolamine mesylate injection for the reversal of anesthesia of the lip and tongue resulting from administration of an introral submucosal local anesthetic containing a vasoconstrictor is recommended for use in dental patients _______ or weighing at least _______.
   a. 5 years or older; 15 kg
   b. 5 years or older; 30 kg
   c. 6 years or older; 15 kg
   d. 6 years or older; 30 kg

31. _______ clinical trials have been conducted to demonstrate the safety and efficacy of phentolamine mesylate for the reversal of soft-tissue anesthesia.
   a. No
   b. A number of
   c. More than 50
   d. none of the above

32. A pediatric Phase II, double-blinded, randomized, multicenter controlled study was conducted in dental patients _______ who had received 2% lidocaine with 1:100,000 epinephrine.
   a. age 2 to 7 years
   b. age 3 to 9 years
   c. age 4 to 11 years
   d. none of the above

33. The functional assessment battery (FAB) includes measurements of _______.
   a. smiling and speaking
   b. drooling
   c. drinking 3 ounces of water
   d. all of the above

34. Lip and tongue palpation involved _______.
   a. prodding the area with a periodontal probe
   b. lightly tapping the area with the pinkie
   c. lightly tapping the area with the index or middle finger
   d. a and c

35. The STAR (soft-tissue anesthesia recovery) questionnaire measures _______.
   a. the patient’s perception of altered function and sensation
   b. appearance
   c. the perceived clinical benefit from reversing soft-tissue anesthesia
   d. all of the above

36. In the Phase III maxillary efficacy trial, the median time to recovery of normal sensation in the upper lip was _______ for phentolamine mesylate patients and _______ for sham patients.
   a. 40 minutes; 120 minutes
   b. 30 minutes; 132.5 minutes
   c. 65 minutes; 145 minutes
   d. none of the above

37. Within _______ of phentolamine mesylate administration, 75% of patients reported normal lip sensation as compared to 25% of patients receiving the sham.
   a. 30 minutes
   b. 60 minutes
   c. 90 minutes
   d. 120 minutes

38. In the Phase III mandibular efficacy trial, the median time to recovery of normal sensation in the lower lip was _______ for phentolamine mesylate patients and _______ for sham patients.
   a. 60 minutes; 110 minutes
   b. 70 minutes; 125 minutes
   c. 70 minutes; 155 minutes
   d. none of the above

39. The median time for return of normal sensation to the tongue was _______ for subjects receiving phentolamine mesylate versus _______ for sham-treated patients.
   a. 30 minutes; 115 minutes
   b. 45 minutes; 125 minutes
   c. 60 minutes; 125 minutes
   d. none of the above

40. The Heft-Parker visual analogue scale measures the patient’s current assessment of _______.
   a. pain at the injection site and procedural site
   b. swelling at the injection site
   c. paresthesia
   d. a and b

41. Visual signs measured during the study included _______.
   a. systolic and diastolic blood pressure in sitting or supine position
   b. systolic and diastolic blood pressure after standing for one minute
   c. respiration, pulse and temperature
   d. all of the above

42. During safety evaluations, _______ differences were found in oral cavity assessments and vital sign measurements between the phentolamine mesylate and the sham groups.
   a. no
   b. some
   c. many
   d. none of the above

43. In a pediatric trial on the use of phentolamine mesylate for the reversal of residual soft-tissue anesthesia, the reduction in median time to normal lip sensation compared to the sham group was _______.
   a. 25 minutes
   b. 30 minutes
   c. 75 minutes
   d. none of the above

44. In a pediatric trial on the use of phentolamine mesylate for the reversal of residual soft-tissue anesthesia, the reduction in median time to normal tongue sensation compared to sham patients was _______.
   a. 15 minutes
   b. 30 minutes
   c. 45 minutes
   d. 60 minutes

45. Phentolamine mesylate is _______ recommended for use in children younger than 6 years of age or weighing less than 15 kg (33 lb).
   a. not
   b. sometimes
   c. strongly
   d. none of the above

46. _______ may occur with the use of phentolamine.
   a. Tachycardia
   b. Cardiac arrhythmias
   c. Bradycardia
   d. all of the above

47. There are _______ adequate and well-controlled studies on the use of phentolamine mesylate in pregnant women.
   a. no
   b. two
   c. several
   d. none of the above

48. _______ and other occurrences can happen with overdosing.
   a. Visual disturbances
   b. Hypoglycemia
   c. Vomiting
   d. all of the above

49. Phentolamine mesylate should be administered following the dental procedure using _______ employed for the administration of the local anesthetic.
   a. the same location(s) and technique(s)
   b. an adjacent location(s) and the same technique(s)
   c. an adjacent location(s) and modified technique(s)
   d. any of the above

50. _______ will benefit from the diminished soft-tissue anesthesia duration associated with phentolamine mesylate administration.
   a. Pediatric patients
   b. Patients with medical conditions requiring strict adherence to a vegan diet
   c. Patients with medical conditions requiring strict adherence to eating regimens
   d. a and c
Phentolamine mesylate for the reversal of residual soft-tissue anesthesia

Educational Objectives

1. List and describe the types of local anesthetics that were introduced to dentistry over time.
2. Describe the time for which residual soft-tissue anesthesia can persist as well as patient perceptions of this.
3. List and describe the safety and efficacy of phentolamine mesylate based on clinical data presented.
4. List the age groups for which phentolamine mesylate can be used, applicable dosing, and describe potential side effects of phentolamine mesylate (OraVerse).

Course Evaluation

Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

1. Were the individual course objectives met?  
   Objective #1: Yes No  
   Objective #2: Yes No  
   Objective #3: Yes No  
   Objective #4: Yes No

2. To what extent were the course objectives accomplished overall?  
   5 4 3 2 1 0

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

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

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

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

7. Was the overall administration of the course effective?  
   5 4 3 2 1 0

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

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

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

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

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