

Modern Dental Pain Control

Stanley F. Malamed

Introduction

Local anesthetics are the most important drugs used in dentistry, forming the backbone of pain control techniques. They also represent the safest and most effective drugs in all of medicine for the control and prevention of pain. The overwhelming majority of anesthetic drugs are central nervous system (CNS) depressants—drugs that do not prevent a painful nerve stimulus from reaching the brain where it is interpreted as pain by the patient. During general anesthesia these drugs depress the brain to the point where consciousness is lost. The nociceptive stimulus evoked by the surgeon travels to the brain where, because the patient is unconscious, they are unable to respond outwardly. However the autonomic nervous system reacts to the stimulus with a brief, hopefully insignificant, elevation in blood pressure, heart rate, and respiratory rate.

Local Anesthetics: Background

Local anesthetics, on the other hand, deposited near a nerve between the surgical site and the brain, set up a chemical roadblock that prevents the pain impulse from ever reaching the brain (Figure 1). The patient's level of consciousness remains unaffected when local anesthetics are administered, unlike the CNS depressants used in general anesthesia. The safety of local anesthetics may be garnered from the following statement attributed to Dr. Leonard Monheim, an icon in the history of dental anesthesiology, "Nobody ever died in the conscious state."

A number of local anesthetics are available for administration in dentistry in the United States. The major difference between these formulations is their expected duration of clinical anesthesia. Drugs are categorized as "short-acting," "intermediate-acting," and "long-acting." Table 1 presents the current local anesthetic formulations available in the United States.

According to the 2002 American Dental Association's Survey of Dental Practice, the typical treatment period for a patient in a general dentistry office is approximately 47 minutes.¹ "Plain" local anesthetics (LAs) provide neither the depth nor duration of anesthesia required for

anything more than short, shallow procedures. In order to provide anesthesia of a depth and duration permitting completion of the dental treatment painlessly, LAs are commonly combined with a vasopressor drug, commonly epinephrine (or levonordefrin in the United States). Vasopressors transiently decrease vascular perfusion at their site of deposition, permitting more LA to diffuse into the nerve thereby providing a longer duration and greater depth of pain control. The duration of soft tissue anesthesia (STA) greatly exceeds that noted for pulpal anesthesia (Table 1) with the patient being dismissed at the conclusion of their treatment with several hours of residual STA.

Though local anesthetics represent the most effective drugs for preventing pain, situations do arise in which clinically effective pain control is frustratingly elusive. Factors modifying the expected duration of anesthesia, usually in a negative manner, are listed in Table 2.

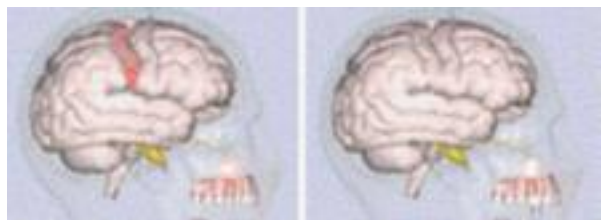


Figure 1a. Impulse from the tooth reaches the brain and the patient interprets it as pain.

Figure 1b. Local anesthetic blocks impulse conduction to the brain.

Dr. Stanley F Malamed, DDS, is a professor of anesthesia and medicine at the School of Dentistry at the University of Southern California, USA

Table 1

Current Local Anesthetic Formulations in the United States and Canada.

Short duration - Plain	Proprietary names	Infiltration	Nerve block	Soft tissue anesthesia	Mgs per cartridge
Lidocaine HCl 2% plain	Xylocaine	5 minutes	Not indicated	2 hrs	36
Mepivacaine HCl 3% plain	Carbocaine Isocaine Polocaine Scandanest	20-30 min	34-45 min	2-3 hrs	54
Prilocaine HCl 4% plain	Citanest Plain	10-15 min	45-65 min	3-4 hrs	72
Intermediate duration - with vasoconstrictor	Proprietary names	Infiltration	Nerve block	Soft tissue anesthesia	Mgs per cartridge
Articaine HCl 4% + epinephrine 1:100,000	Septocaine Zorcaline	60 min	Up to 120 min	3-5 hrs	68
Articaine HCl 4% + epinephrine 1:200,000	Septocaine	60 min	Up to 120 min	3-5 hrs	68
Lidocaine HCl 2% + epinephrine 1:50,000	Lidocaine Lignospan Standard Octocaine 50 Xylocaine	55-65 min	80-90 min	3-5 hrs	36
Lidocaine HCl 2% + epinephrine 1:100,000	Lidocaine Lignospan Standard Octocaine 100 Xylocaine	55-65 min	80-90 min	3-5 hrs	36
Mepivacaine HCl 2% + levonordefrin 1:20,000	Carbocaine Isocaine 2% Polocaine Scandanest 2%	40-60 min	60-90 min	3-5 hrs	36
Prilocaine HCl 4% + epinephrine 1:200,000	Citanest Forte	35-45 min	50-70 min	3-6 hrs	72
Long duration	Proprietary names	Infiltration	Nerve block	Soft tissue anesthesia	Mgs per cartridge
Bupivacaine HCl 0.5% + epinephrine 1:200,000	Marcaine Vivacaine Bupivacaine	Up to 7 hrs	Up to 7 hrs	Up to 12 hrs	9

Probably the two most significant of these factors are local anesthetic technique and the normal distribution (bell-shaped) curve, while the mandibular molar region represents the area where the overwhelming majority of these problems in pain control develop.² (See Table 3).

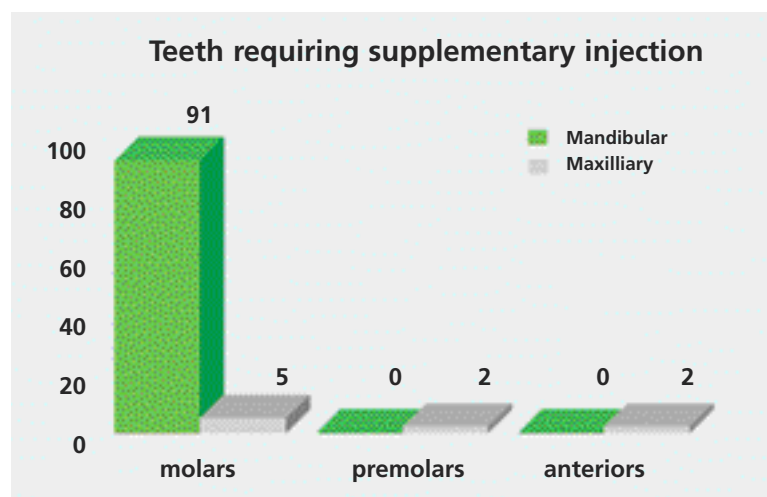
The inferior alveolar nerve block (IANB), the traditional injection used to anesthetize mandibular teeth and soft tissues has the greatest failure rate on any of the major nerve blocks administered in the human body. Yet, this injection represents the most used nerve block technique

Table 2

Factors Modifying Expected Duration of Anesthesia.

TECHNIQUE	– accuracy in deposition of drug
‘BELL-SHAPED’ CURVE	– individual variation in response to drugs
ANATOMY	– anatomical differences between patients
STATUS OF TISSUE AT DEPOSITION SITE	– infection, hyperemia decrease expected duration
TYPE OF INJECTION	– Nerve block longer duration than infiltration
CHRONOBIOLOGY	– Time of day influences effectiveness of drug

Table 3
Difficulty in Providing Clinically Adequate Pain Control.



in dentistry. Innovative techniques, such as the Gow-Gates mandibular block,^{3,4} the Akinosi-Vazirani closed-mouth mandibular block,⁵ periodontal ligament injection (PDL),⁶ and intraosseous anesthesia⁷ have been developed or reintroduced as means of improving upon the dismal success rate of the IANB.

Successful though these may be, occasional problems are still noted in providing pain-free dentistry for our patients. A collateral problem is that following the administration of a local anesthetic, STA persists for periods ranging from 2 to 12 hours, interfering with the patient's life style, increasing the risk of self-inflicted injury, and potentially leading to urgent medical situations such as hypoglycemia.

The remainder of this paper will discuss two relatively new additions to the dental pain management armamentarium: the local anesthetic, articaine HCl and the local anesthetic reversal agent, phentolamine mesylate.

Articaine HCl, synthesized in the early 1970s, was introduced to dentistry in Germany in 1976 as the proprietary drug Ultracain. Today articaine HCl is available worldwide in more than 135 countries as a 4% solution with epinephrine 1:100,000 and 1:200,000. Articaine HCl, introduced into the United States in 2000, provides approximately 60 minutes of pulpal anesthesia and between 3 to 5 hours of STA. (See Table 1). Articaine HCl has been hailed (anecdotally) by many practicing dentists as a local anesthetic that, in their words: "worked faster," "worked better," "I don't miss as often," and "hard to get numb patients are easy to get numb with articaine." Yet, double-blinded, randomized, controlled-clinical trials

in the United States demonstrated that articaine HCl was as safe and as effective as lidocaine HCl, the drug to which it was compared.⁸⁻¹⁰ Indeed, the overwhelming majority of clinical trials comparing articaine HCl to other LAs (mepivacaine, prilo-caine) showed similar results.¹¹⁻¹² It is only in recent years that several well-controlled clinical trials have demonstrated a superiority of articaine HCl to other LAs in certain clinical situations.

One such situation is in providing pulpal anesthesia in the mandible, specifically to mandibular molars, the most difficult teeth to anesthetize on a consistent basis. In the first study, a cartridge of either lidocaine HCl with epinephrine 1:100,000, or articaine HCl with epinephrine 1:100,000, was injected in the buccal fold adjacent to the first mandibular molar.¹³ An electronic pulp tester (EPT) was used to evaluate efficacy of anesthesia (EPT every 2 minutes until 30 minutes post injection. Success was measured as absence of pulp sensation on 2 consecutive maximal pulp tester stimulations (80 uA). Kanaa et al,¹³ found a 64.5 success with articaine HCl compared with 37.7% for lidocaine HCl ($p = 0.008$). A similar study by the Ohio State University Postdoctoral Endodontic group demonstrated remarkably similar results.¹⁴ Testing the second and first molars, and second and first premolars, with EPT every 3 minutes and using the same criteria for success as Kanaa et al; articaine HCl provided significantly greater degrees of pulpal anesthesia than lidocaine HCl for all teeth tested. (See Table 2).

Another potential advantage possessed by articaine HCl is its 27 minute distribution half-life. Other amide local anesthetics possess half-lives of approximately 90 minutes.¹⁵ Blood levels of articaine HCl decrease

Table 4

Success of Articaine HCl + Epinephrine 1:100,000
by Mandibular Infiltration Versus Lidocaine HCl + Epinephrine 1:100,000.

Tooth	% (#/total) with anesthetic success		P value
	Articaine HCl	Lidocaine HCl	
2nd molar	75 (45/60)	45 (27/60)	.0001*
1st molar	87 (52/60)	57 (34/60)	.0001*
1st molar	64.5 (20/31)	38.7 (12/31)	.008*
2nd premolar	92 (55/60)	67 (40/60)	.0001*
1st premolar	86 (59/57)	61 (35/57)	.0001*

- There were significant differences (P<.05) between the articaine and lidocaine formulations as analyzed by means of logistic regression
- Data compiled from references 13 and 14

significantly quicker than other LAs providing several potential benefits: decreased risk of overdose (toxic reaction) from overadministration (but not from rapid in-travascular injection), and increased utility in the nursing mother.

All local anesthetics are safe drugs when used properly, however drug overdose remains the most likely drug-related complication associated with their administration. A Medline search (August 3, 2008) dating back to 1975 did not find any reported death associated with the administration of articaine in either dentistry or medicine (272 cited papers).

The nursing mother in need of dental care that is potentially painful will require a local anesthetic. A common question from this patient is: "Will the drug be found in my milk?" The answer is yes. Before the doctor or hygienist can add, "But it is safe for your infant," the mother will say, "Then I don't want it." Local anesthetics will be found in decreasing amounts in the blood (and therefore in the milk) for a period equal to approximately 6 times the elimination half-life of the drug. (At 6 half-lives the blood level of a drug has decreased by 98.5%). Lidocaine HCl, mepivacaine HCl and prilocaine HCl, with half-lives of about 90 minutes will be found in the blood and milk for approximately 9 hours following administration. Articaine HCl, with a half-life of 27 minutes will be in the blood and milk for about 162 minutes (2 hours and 42 minutes) making it easier to use in those situations where LAs are required. The nursing mother can pump and store milk prior to receiving the LA.

Though articaine HCl has become a popular LA in most

countries, there exists a sense amongst some people that its use is associated with a higher risk of paresthesia. Haas and Lennon¹⁶ published results of voluntary reports to an insurance plan in Ontario, Canada indicating that 4% LAs have a greater reported incidence of paresthesia than 2% or 3% LAs. Though admittedly a preliminary survey, many have interpreted their results as the "gospel chipped in stone"—as definitive evidence that 4% LAs in general, and articaine HCl in particular, are associated with a greater risk of paresthesia. It has been recommended by some "experts" and agencies that articaine HCl not be administered by inferior alveolar nerve block (IANB) because of this increased risk.¹⁷⁻¹⁹

In response to the Hillerup paper,¹⁷ the Pharmacovigilance Committee of the European Union (the equivalent of the Food and Drug Administration in the United States) reviewed articaine HCl. They concluded that the "safety profile of the drug (articaine) has not significantly evolved since its initial launch (1998). Thus, no medical evidence exists to prohibit the use of articaine according to the current guidelines listed in the summary of product characteristics" (the drug package insert).²⁰

In 2007, Pogrel²¹ reported on 53 cases of LA-related paresthesia referred to him in northern California for evaluation. Lidocaine HCl had been administered in 35% of the cases evaluated, articaine HCl in 30% and prilocaine HCl in 30%. When adjusted for the percentage of sales for each of the drugs, Pogrel concluded: "...based on the figures we have generated from our clinic we do not see any disproportionate nerve involvement from articaine."

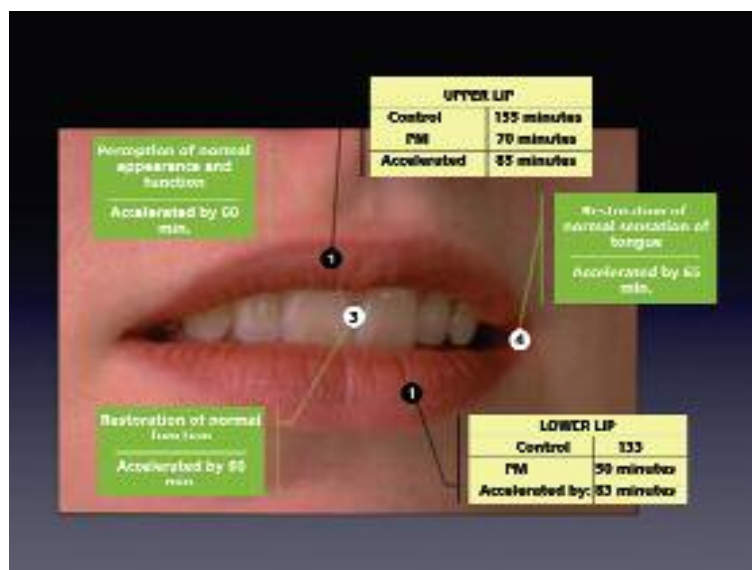


Figure 2. Summary of phentolamine mesylate clinical trials. Data is combined from references 25 and 26. (Courtesy of Suzete Brasil, Erica Dicterow, Fariba Neumann, Joan Ong, dental hygiene students at the University of Southern California School of Dentistry, 2008).

Phentolamine Mesylate: An LA Reversal Agent

As noted above and in Table 1, the duration of soft tissue anesthesia (STA) is considerably longer than that of pulpal anesthesia and of the duration of the typical dental appointment. Residual STA can be of benefit to the patient in the post-treatment period when the dental procedure is traumatic and associated with postoperative pain. Examples include endodontic procedures, periodontal surgery, oral surgical procedures, implants, or other extensive dental interventions. However, the vast majority of dental procedures, though requiring pain prevention through LA administration, are not associated with any degree of postoperative pain. The continued presence of STA into the post-treatment period is oftentimes unwanted and even undesirable.

Reports in pediatric dentistry indicate that up to 13% of patients suffer traumatic injury to their still anesthetized soft tissues following LA administration in the dental office.²² More commonly, residual STA is simply more of an inconvenience or annoyance to the patient and doctor than a risk. Patients feel that residual STA interferes with their normal daily activities in 3 areas: perceptual (perception of altered physical appearance), sensory (lack of sensation), and functional (diminished ability to speak, smile, drink, and control drooling).²³ Many dental patients 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 lip and/or tongue were still

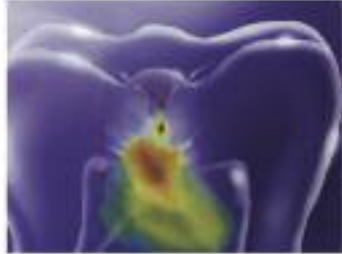
numb. The request of "Doctor, can't you make the numbness go away faster?" has been uttered by patients to most doctors.

Phentolamine mesylate (0.4 mg, packaged in a 1.7-mL dental cartridge) has been developed to accelerate the return of intraoral and perioral sensations after the completion of routine nonsurgical dental procedures. Phentolamine is a nonselective alpha-adrenergic blocking agent that has been available in the United States since 1952. Although it was originally developed for the treatment of hypertension, the currently FDA-approved intravenous/intramuscular formulation is indicated for the treatment of dermal necrosis resulting from inadvertent extravasation of norepinephrine, and for the diagnosis and treatment of patients with pheochromocytoma—a tumor of the adrenal medulla with which excessive catecholamines may result in severe hypertension. Like other alpha adrenergic blocking agents, phentolamine's primary effect is vasodilation.

Following the administration of a LA with an adrenergic vasoconstrictor, subsequent injection of phentolamine at the same location has been found to induce a rapid return of normal intraoral and perioral sensations.²⁴⁻²⁶ A phase 2, double-blind, placebo-controlled clinical trial of 122 patients, who had received mandibular or maxillary LA for routine restorative or periodontal maintenance procedures, first reported that phentolamine mesylate 0.4 mg decreased the median duration of lip anesthesia by 85 minutes or 54.8% compared to placebo injections

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($P < 0.0001$).²⁴ In those patients receiving mandibular injections, the median duration of tongue anesthesia was reduced by 31.5 minutes or 30% ($P > 0.0001$) in the phentolamine group compared to the placebo. For a small subset of study participants requiring 2 local anesthetic injections to complete their dental procedures, the administration of 0.8 mg of phentolamine was also found to be efficacious and equally well tolerated.²⁴

The clinical findings of 2 additional clinical trials enrolling 484 adults and 152 pediatric patients reported similar reductions in soft tissue anesthesia following the administration of phentolamine^{25,26} (Figure 2).

A New Drug Application (NDA) was approved in May 2008 by the FDA for marketing under the name OraVerse (Novalar Pharmaceuticals) which will be available in early 2009.

Clinical Use Of Phentolamine Mesylate

The dental patient receives a LA injection containing a vasoconstrictor at the onset of their treatment. The choice of drug is determined by the expected duration of pulpal anesthesia required to complete the dental procedure (Table 1). At the conclusion of the "traumatic" portion of the dental procedure (eg, the procedure necessitating pulpal anesthesia, such as drilling) phentolamine mesylate is injected, on a one-to-one cartridge basis, into the same site as the previously injected LA (eg, a left inferior alveolar nerve block injection when treating the mandibular left quadrant).²⁷

For adults the proposed dosage is 1 to 2 cartridges of phentolamine mesylate (a dose of 0.4 mg to 0.8 mg), while for children the proposed dosage is 0.5 to 1 cartridge (0.2 mg to 0.4 mg).²⁷ Phentolamine mesylate produces localized vasodilation, increasing perfusion at the site of deposition, and a more rapid redistribution of the LA from the injection site into capillaries and venules and away from the oral cavity.²⁴

Let's now discuss a clinical example of how reversal of anesthesia benefits a patient. In the present environment, without a LA reversal agent, the patient arrives for a 1-hour dental appointment in mid-to-late afternoon. As the procedure requires tooth preparation, the dentist administers 2% lidocaine with epinephrine 1:100,000 via an inferior alveolar nerve block. Successful anesthesia is achieved. Treatment is completed in approximately 45 minutes. The patient leaves the office approximately 1 hour after having received the LA with residual STA of the lip and tongue. Apart from the fact that the patient still feels strange because of the residual

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numbness (eg, "my lip feels fat"), the patient will be unable to eat. And if he does, he will be unable to eat without an increased risk of traumatic soft-tissue injury, when dinner is served several hours later.

With the administration of phentolamine mesylate at the conclusion of the traumatic portion of the treatment, or immediately after the dental procedure, residual STA has completely resolved by the time dinner is served.

Candidates for Local Anesthetic Reversal

A majority of dental treatments today are not traumatic enough in nature as to require a patient to leave the dental office with residual STA that commonly persists for many hours before gradually resolving. These procedures include conservative dental restorations and nonsurgical periodontics, 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.

Conclusion

Local anesthetics form the backbone of pain control in dentistry. The recent additions of articaine HCl and phentolamine mesylate to our armamentarium has allowed the dentist to achieve a greater level of successful anesthesia in the mandible (articaine HCl) and to aid the patient in recovering from the residual effects of soft tissue anesthesia (phentolamine mesylate).

Disclosure: Dr. Malamed is a paid consultant for Novalar Pharmaceuticals, Inc, and Septodont, Inc. He is an unpaid consultant for Milestone Laboratories

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