Local Anesthetics: Dentistry's Most Important Drugs, Clinical Update 2006

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ABSTRACT

Local anesthetics are the safest and most effective drugs in medicine for the control and management of pain. They also represent the most important drugs in dentistry. Today, dentistry has a spectrum of local anesthetics that permit pain control to be tailored to the specific needs of the patient: short-, intermediate-, and long-acting drugs. Bupivacaine has become a standard part of the armamentarium for postsurgical pain control while articaine has become the second-most used local anesthetic in the United States since its introduction in 2000. Despite an increase in anecdotal reports of paresthesia since articaine's introduction there is, as yet, no supporting scientific evidence.

Local anesthetics form the backbone of pain control techniques in dentistry. Their introduction, by Karl Koller and Sigmund Freud (topically), and William Halsted (injectably) in 1885, revolutionized the practice of surgery, both dental and medical. Prior to their introduction, general anesthesia, was the only viable method of managing surgical pain. Administration of drugs that depressed the central nervous system to the point that the patient lost consciousness allowed the surgeon to successfully complete otherwise painful and potentially lethal procedures. During general anesthesia, the pain impulse propagated during surgical manipulation is carried along neurons to the patient's brain. Because of central nervous system depression, the patient is unable to outwardly react to this stimulation, e.g., no visible movement. However, vital functions — such as blood pressure, heart rate — and respiratory rate do respond to this nociceptive stimulus. Slight elevations in vital signs are noted at the time of incision and other manipulations.

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BY THE EARLY 1900s, REPORTS OF SERIOUS ADVERSE REACTIONS TO COCAINE AND EPINEPHRINE HAD APPEARED IN BOTH LAY AND MEDICAL LITERATURE.

To minimize these responses, increased concentrations of inhaled anesthetic gases or larger doses of injected drugs must be used. However, administration of larger doses is associated with an increased risk of potentially significant adverse drug effects.

The introduction of an injectable local anesthetic, cocaine with epinephrine 1:50,000, permitted surgeons for the first time to operate painlessly on a conscious human being. In 1885, Dr. William Stewart Halsted (1852-1922) administered an inferior alveolar nerve block for the surgical removal of the nerve. Not surprisingly, cocaine was hailed as a "wonder drug." From 1885 until the beginning of the 20th century, cocaine with epinephrine was the drug of choice in dental and surgical pain control. However, by the early 1900s, reports of serious adverse reactions to cocaine and epinephrine had appeared in both lay and medical literature. Halsted himself became addicted to cocaine, injecting himself as a means of maintaining energy for his ever-increasingly busy schedule of surgery, writing, and lecturing. Cocaine is unique amongst all local anesthetics in that it possesses stimulatory actions on the cardiovascular system, producing elevations in heart rate and blood pressure, as well as sensitizing the myocardium and provoking potentially lethal dysrhythmias, e.g., ventricular fibrillation. As cardiopulmonary resuscitation did not exist until 1960, the occurrence of cardiac arrest was uniformly fatal.

Development of Local Anesthetics (Esters)

In 1904 in Germany, Alfred Einhorn (1856-1917) synthesized procaine. Introduced into medicine and dentistry at that time, the drug became the most widely used local anesthetic in the world. Its proprietary name, Novocain, remains synonymous with the lay public as "the" dental local anesthetic.

Procaine, like cocaine, is an amino-ester local anesthetic. The ester-type local anesthetics work, as do virtually all other local anesthetics, by diffusing through the lipid-rich nerve membrane and then blocking Na^+ channels, thus producing a nondepolarizing nerve block. Clinical activity, anesthesia, is terminated when the drug diffuses out of the Na^+ channels entering into the cardiovascular system where it is then redistributed to other areas in the body. Biological transformation, also known as metabolism and detoxification, of the amino-esters starts with their entry into the cardiovascular system as the enzyme plasma pseudocholinesterase cleaves the molecule. Procaine became the "standard of comparison," the "gold standard" to which all new local anesthetics were compared.

Procaine with epinephrine was popular because its duration of pulpal anesthesia met the needs of the dental profession in the early to mid-1900s. With foot-treadle handpieces, the typical dental appointment was approximately 30 minutes in length, the duration of pulpal anesthesia expected with procaine and epinephrine (1:50,000).

Though other amino-ester local anesthetics, such as tetracaine and propoxycaine, were available, procaine remained the predominant local anesthetic used in both dentistry and medicine.

Development of Local Anesthetics (Amides)

By the mid-1940s, dentistry was becoming disgruntled with the available local anesthetics. Introduction of the belt-driven handpiece, as well as other therapeutic advances, led to longer treatment periods and the realization that procaine + epinephrine was no longer an adequate anesthetic, both in duration and depth of anesthesia, for many dental procedures. Additionally, procaine possesses the slowest onset of the clinical available local anesthetics, approximately 10 to 15 minutes. One final factor came to bear, the development of allergy to the broad class of ester-type local anesthetics.

In 1943 in Sweden, Nils Lofgren synthesized a new class of local anesthetic, developing lidocaine, the first amino-amide. Marketed in 1948 under the proprietary name Xylocaine, it quickly became a favorite of the dental profession, replacing procaine as the "gold standard." Lidocaine's onset of action was measurably faster (three to five minutes); its duration of anesthesia (pulpal) was longer and more profound; and it provided more consistently reliable anesthesia than did the esters.

In 1960, the second amide was introduced, mepivacaine (Carbocaine), followed in 1965 by prilocaine (Citanest).

Use of the esters declined precipitously during this time and, in 1996, the last remaining formulation of an ester local anesthetic (procaine + propoxycaine) in dental cartridges ceased to be manufactured.

Lidocaine, mepivacaine and prilocaine, combined with a vasopressor (epinephrine or levonordefrin) provide reliable and profound pulpal anesthesia for approximately 60 minutes (with a duration of soft tissue anesthesia lasting from three to five hours). As the dental profession turned to high-speed handpieces and more involved procedures, the length of a typical appointment increased. The American Dental Association's Annual Survey of Dental Practice in 2002 noted that the typical general dentistry patient received treatment for approximately 44 minutes.[1]

TO DATE, ONLY ONE CLINICAL TRIAL HAS DEMONSTRATED ANY SUPERIORITY OF ARTICAINE TO ANY OTHER LOCAL ANESTHETIC.

These three amide local anesthetics meet the anesthesia needs of the vast majority of dental patients and remain amongst the most popular local anesthetics used in dentistry today. (Mepivacaine "plain" provides pulpal anesthesia of from 20 to 40 minutes along with soft tissue anesthesia lasting approximately two to three hours).

The 1970s saw an increase in the number of surgical procedures, along with an increase in the length of many other dental procedures. Along with the surgery came a pressing need for effective postsurgical pain control. Dentistry turned to two local anesthetics, bupivacaine and etidocaine, both of which had been developed in medicine to aid in exactly this area, providing up to 12 hours of soft tissue anesthesia. Initially available only in multiple dose vials, bupivacaine 0.5 percent with epinephrine 1:200,000 (proprietary name: Marcaine) was released in dental cartridges in 1983, followed in 1988 by etidocaine 1.5 percent with epinephrine 1:200,000 (Duranest). Though accounting for only a small percentage of dental local anesthetic usage in the United States and Canada, these drugs have been extremely useful, in conjunction with orally administered nonsteroidal anti-inflammatory drugs, in the prevention or management of postoperative pain. Bupivacaine became the more preferred formulation and, in 2002, etidocaine was withdrawn from the U.S. market.

In 1969, carticaine was synthesized and, in 1976, introduced in German dentistry. The generic name was changed to articaine several years later. Articaine, with epinephrine, provides a duration of pulpal and soft tissue anesthesia similar to that noted with lidocaine, mepivacaine and prilocaine with vasopressor, approximately one hour pulpal and three to five hours of soft tissue. Introduced into Canada in 1983, and the United States in 2000, articaine has become a very popular local anesthetic.

Currently Available Local Anesthetic Formulations

Table 1 lists the currently available dental local anesthetic formulations in North America and **Table 2** lists the approximate share of the U.S. dental market for each local anesthetic.

Bupivacaine

At this time, bupivacaine is the only long-acting local anesthetic available in dental cartridges in North America. Despite its relatively slow onset (six to 10 minutes) bupivacaine is a very important local anesthetic in the prevention of postoperative (e.g. surgical) pain. Administered in conjunction with oral (po) NSAIDs it is possible, and highly likely, that the perioperative period for most patients will be comfortable. A recommended regimen is presented in **Table 3**.

In May 2006 it was announced that Marcaine would no longer be available in dental cartridges, leading to a significant degree of consternation amongst dental surgeons.[3] Though its proprietary form, Marcaine, remains available in a multiple dose vial, the drug is once again available in dental cartridges, as the generic drug bupivacaine (0.5 percent with 1:200,000 epinephrine), from Hospira. It may be ordered from either Patterson Dental (www.pattersondental.com) or Sullivan-Schein (www.sullivanschein.com). Marcaine, in dental cartridges, was scheduled to become available again in November 2006.

Articaine

Articaine under its proprietary names Septocaine (United States), Zorcaine (United States), Ultracaine (Canada), Septanest (Canada) and Astracaine (Canada) has become a very popular local anesthetic in North American dentistry since its introduction into Canada in 1983 and the United States in 2000. Little to no evidence-based medicine exists demonstrating any superiority of articaine over other available local anesthetics. However dentists in clinical practice have claimed that articaine possesses properties that other local anesthetics don't. Included in these admittedly anecdotal reports are claims that articaine 1) works faster, 2) works "better," 3) "I don't miss as often," and 4) "gets patients numb when other local anesthetics fail."

Since its introduction in Germany in the early 1970s, articaine has been compared in double-blinded, randomized, controlled clinical trials to each of the other available local anesthetics. To date, only one clinical trial has demonstrated any superiority of articaine to any other local anesthetic.[4] Phase 3 clinical trials performed at 29 sites in the United States and United Kingdom in the late 1990s compared articaine to lidocaine in more than 1,400 patients undergoing dental care.[5,6] The summary of the trials stated there were no clinically significant differences between articaine and lidocaine, and concluded that articaine was a "safe and effective local anesthetic" for dentistry.

Yet, despite a lack of evidence demonstrating its superiority articaine continues to become increasingly popular in the United States. Endodontists have become enamored with the drug as a more definitive means of achieving profound anesthesia to permit painless pulpal extirpation in "hot" mandibular molars — the most difficult teeth to anesthetize successfully, yet again in the absence of any published clinical trials demonstrating this advantage.

Table 1

CURRENTLY AVAILABLE DENTAL LOCAL ANESTHETIC FORMULATIONS

Local anesthetic	%	Vasopressor	Mgs. LA/ cartridge	Onset, minutes	Expected duration	
					Pulpal, minutes	Soft tissue, hours
Articaine	4	Epinephrine 1:200,000 1:100,000	 72 72	 2-3 2-3	 60 60	 3-5 3-5
Bupivacaine	0.5	Epinephrine 1:200,000	9	6-10	90-180	3-12
Lidocaine	2	 Epinephrine 1:50,000 / 1:100,000	36 36	3-5 3-5	10 60	1-2 3-5
Mepivacaine (Canada)	3 2	 Levonordefrin 1:20,000 epinephrine 1:100,000	54 36 36	3-5 3-5 3-5	20-40 60 60	2-3 3-5 3-5
Prilocaine	4	 Epinephrine 1:200,000	72 72	3-5 3-5	5-10 infiltration 40-60 nerve block 60-90	2-3 3-8

One reason for this difficulty in demonstrating articaine's alleged superiority to other local anesthetics is simply that the other available drugs are very effective in general. Unlike in the late 1940s when the "new" drug, lidocaine, was compared to the "old" drug, procaine, and was shown to be demonstrably superior in all clinical measurements, the amide local anesthetics in use today are "darned good." Indeed, prior to the introduction of articaine in 2000 (United States) was there, in dentistry in the United States, an urgent need for "better" local anesthetics? The answer is a definite "No."

The occasional patient might prove difficult to "numb," and infected mandibular molars might be difficult to satisfactorily anesthetize, problems which were much more common prior to the introduction of the amides. But overall, dentists were quite satisfied with the rapid onset, depth (profoundness), duration, and consistency (reliability) of anesthesia produced by the entire class of amide local anesthetics. It is difficult, if not impossible, to demonstrate to a level of statistical significance (evidence-based medicine) in an economically sound clinical trial that articaine is superior to any other commonly used amide local anesthetic.

Along with the "good" there is always the "bad," and articaine is no exception. Haas and Lennon published the results of voluntary reports by dentists to an insurance plan in Ontario, Canada, concluding that 4 percent local anesthetics have a greater reported incidence of paresthesia than 2 percent or 3 percent local anesthetics.[7] Though admittedly a preliminary survey, many have taken the results as the "gospel chipped in stone" — as definitive proof that 4 percent local

Table 2

LOCAL ANESTHETIC USAGE IN THE UNITED STATES, 2005 (ESTIMATED)

Local anesthetic	% of U.S. market (estimated)
Lidocaine HCl	47
Articaine HCl	26
Mepivacaine HCl	15
Prilocaine HCl	6
Bupivacaine	1

Data from Septodont, Inc. (October 2006)

Table 3

PERIOPERATIVE PAIN MANAGEMENT REGIMEN

NSAID po one hour prior to scheduled start of procedure: e.g., ibuprofen 800 mg[2]
LA of choice for periprocedural pain control: e.g., articaine, lidocaine, mepivacaine or prilocaine, with vasopressor
Administration of bupivacaine: at surgical site, at the conclusion of the procedure, if the procedure is prolonged (e.g., one hour or more) at surgical site, immediately following administration of LA for pain control, if the procedure is of short duration (<30 minutes)
Continuation of NSAID po for recommended duration of days e.g., ibuprofen 800 mg tid
Postoperative telephone call to patient early evening of surgery Review postoperative instructions

anesthetics in general, and articaine in particular, are associated with a greater risk of paresthesia. At this time, there is absolutely no scientific evidence to demonstrate there is a greater risk of paresthesia associated with administration of a 4 percent local anesthetic.

All reports of paresthesia have been anecdotal. Evidence-based research does not exist.

When evaluating reports of paresthesia following local anesthetic administration (in nonsurgical cases), first determine the distribution of nerve involvement. The overwhelming majority of reported instances of paresthesia occur in the mandible following a traditional inferior alveolar nerve block. A Medline search for reports of paresthesia following maxillary dental procedures from 1966 to 2006 produced but one paper, reporting paresthesia of the incisive papilla following the P-ASA injection.[8] In the Haas-Lennon survey, all of the 143 reported nonsurgery-related cases of paresthesia were mandibular, with the tongue (lingual nerve) most frequently involved.[7] Pogrel similarly reported that although almost all reported paresthesia cases in dentistry develop following inferior alveolar nerve block, more than 70 percent involve the lingual nerve.[9,10] Forty-two of 52 Danish patients reported by Hillerup and Jensen demonstrated damage to the lingual nerve, which was associated with all available local anesthetic formulations.[11] Twelve reported injury to the inferior alveolar nerve.

Though there are possible causes for this preponderance of reported lingual nerve paresthesia, "there appears to be no documentation in the literature as to possible explanations for this."[10]

Some possible etiologies include: 1) direct needle trauma to the lingual nerve; 2) hemorrhage, either extraneural or intraneural; 3) edema, either extraneural or intraneural; and 4) chemical neurotoxicity of the local anesthetic drug, vasopressor, and/or other ingredients of the local anesthetic cartridge.

Paresthesia has not been reported following alternative mandibular nerve block techniques such as the Gow-Gates or Vazirani-Akinosi (closed mouth) mandibular nerve blocks.

Articaine is administered frequently in nondental surgeries, such as in ophthalmology, orthopedic surgery, and spinal anesthesia.[12-14] There are no reported cases of paresthesia in the medical literature[15] (Medline search 1966-2006).

In a recent review of local anesthetic-associated paresthesia, Missika and Khoury stated that "a clear causal relationship has not been established in the literature between the anesthetic agent and neurological complications, such as paresthesia."[16]

Given the present level of scientific evidence or, more accurately, the lack thereof, linking 4 percent local anesthetics with an increased risk of neurotoxicity, it seems, to this author, that advisories to dentists from agencies suggesting that it might be prudent to avoid the use of articaine in mandibular nerve blocks is unjustified at this time.[17,18]

However, as in all dental treatments and therapies, it is ultimately the doctor who must make the decision as to whether or not to use a 4 percent local anesthetic, such as articaine, in inferior alveolar (mandibular) nerve block anesthesia. This decision should follow assessment of the benefits to be accrued from use of the drug versus the potential risks associated with its administration. Only when, in the mind of the doctor, the benefit clearly outweighs the risk should the drug be administered.

Remember, that prior to the introduction of articaine into the United States in 2000, local anesthesia in dentistry was not a problem. Successful pain control can still be achieved with other local anesthetics if the doctor feels the risk outweighs the benefit.

Summary

Local anesthetics represent dentistry's most important drugs. Their introduction revolutionized the practices of both dentistry and medicine. Local anesthetics are the safest and the most effective drugs in all of medicine for the prevention and management of pain in the perioperative period.

The amide local anesthetics available today provide the doctor with a broad range of durations of action, from short: (mepivacaine 3 percent) to long (bupivacaine 0.5 percent + epinephrine 1:200,000), as well as a number of formulations providing approximately one hour of pulpal anesthesia.

Bupivacaine, a long-acting local anesthetic, is an important component in the regimen for the management of postoperative pain.

Articaine, the most recent addition to the dental local anesthetic armamentarium, has become a very popular drug primarily as a result of anecdotal clinical reports from doctors using it who find it to have properties not observed in the more traditional local anesthetics. Allegations that 4 percent local anesthetics are associated with a greater risk of paresthesia are based solely on anecdotal reports and have no scientific justification. ■■■■

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