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What's New in Local Anesthesia?

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Pain control is an absolutely essential part of the successful practice of dentistry in the 1990s. Indeed, it is difficult to imagine most dental care being tolerated without adequate pain control. Images conjured up of such situations include the infamous scene in the 1976 movie *Marathon Man,* in which Sir Laurence Olivier attempts to determine "Is it safe?" from Dustin Hoffman through the use of a dental drill entering into the pulp of an unanesthetized tooth. Seconds after Hoffman's screams stop, Olivier applies oil of cloves (eugenol) to the tooth, and the pain ceases instantly. "The choice is yours," he tells Hoffman, "pain or relief."

Dentistry is fortunate in that it possesses an abundance of excellent agents for the relief of perioperative and postoperative pain associated with the delivery of dental care. The category of drugs known as local anesthetics serves us extremely well. Local anesthetics represent, as Dr. Edward Driscoll so aptly stated, the backbone of pain control techniques in dentistry. Other techniques of pain control may come and go, but the tried and true techniques of local anesthesia and local anesthetic drugs withstand these temporary challenges, and continue to be the first technique called upon by dentists worldwide when pain control is necessary.

In this paper, I will discuss three aspects of local anesthetic drugs: a brief review of their development, current trends in the use of local anesthetics, and future developments in the area of local anesthetic drugs.

DEVELOPMENT OF LOCAL ANESTHETICS

It is well known that the development of local anesthetics began with the introduction of coca leaves from South America, where they had been used among the religious and political aristocracies of Incan societies.[1] Later, in the 16th century after Franscisco Pizzaro and his conquistadores destroyed the Incan civilization, the lower classes and slaves were paid off in coca leaves as a means of increasing and prolonging their low-cost, high-output labor. In 1859, the Italian physician Paolo Mantegazza declared coca leaves to be a "new and exciting weapon against disease." Coca was brought to Vienna, Austria, for examination by Friedrich Wohler. Albert Niemann, a graduate student of Wohler's, isolated the alkaloid cocaine. On heating in hydrochloric acid, benzoic acid, methyl alcohol, and ecgonine (a little known base) were formed. The Merck Company shortly thereafter gave ecgonine to Sigmund Freud for clinical trials.

In 1880, von Anrep[2] published an extensive paper describing the physiologic and pharmacologic effects of cocaine on animals. He described cocaine's topical anesthetic action on mucous membranes and the anesthetic action when injected beneath the skin. It was not until the introduction of cocaine into the United States that Freud became interested in its clinical properties. In *Uber Coca* (1884), Freud reviewed coca's history and the therapeutic actions and uses of cocaine. He became an avid enthusiast, experimenter, and user of cocaine.

Freud received a cocaine kit from Merck, and he soon began experiments upon himself and Carl Koller, an ophthalmology intern in Vienna. On swallowing cocaine they noted its numbing action upon the tongue. Koller was looking to find a drug that would anesthetize the cornea. Having previously failed with morphine and chloral bromide, he tried cocaine. In the summer of 1884, with Freud in Hamburg, a drop of cocaine solution was instilled into the conjunctival sac of a frog. In a minute or so "the frog allowed his cornea to be touched and he also bore injury of the cornea without a trace of reflex action or defense." Equally favorable tests were performed on a rabbit and a dog.[2] Koller and Joseph Gartner next "trickled the solution under each other's lifted eyelids." Touching the cornea with the head of a pin, both stated jubilantly that "I can't feel anything." The findings were reported in Hamburg on September 15th, with Koller giving Freud full credit for his inspiration.

James Leonard Corning, a neurologist from New York, quickly picked up on this new technique and applied an analytical approach to regional anesthesia in humans. In 1886, Corning published the first textbook on local anesthesia.[3]

Alfred Einhorn, one of the first pharmaceutical chemists, spent years evaluating cocaine and other local anesthetics.[4] He stated in 1899 that (referring to Koller's use of cocaine) "since that time cocaine has been used fre-

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quently despite its numerous disadvantages, namely its great toxicity, the short duration of anesthesia, the impossibility of sterilizing the solution, its high cost, and so on—all factors which stimulated chemists to seek a substitute for cocaine which is free of its disadvantages or at least possesses them to a lesser degree." Such considerations have continued to influence the synthesis of new anesthetics to the present time.*

Einhorn synthesized procaine in 1904, following synthesis of a number of compounds that lacked suitable anesthetic properties (Eucaine, Orthoform, Nirvanine, Holocaine). It was Heinrich Braun, however, who first published a description of procaine in 1905.[5] Procaine became the most widely used local anesthetic until the introduction of the amide lidocaine, prepared by Löfgren in the 1940s. Such was the popularity of procaine, that to this day, most patients and many doctors (unfortunately) still use the name "Novocain" as a generic term for any local anesthetic.

The first amide local anesthetic was dibucaine (Percaine, Nupercaine, Cinchocaine), synthesized in 1929.

CURRENT TRENDS IN LOCAL ANESTHETIC DRUGS

With the clinical introduction of lidocaine in 1948, a new class of local anesthetic agents, the amides, quickly became popular. In the ensuing years this group of drugs has, for all intents and purposes, replaced the esters as the drugs of choice for pain control in dentistry. Mepivacaine (1956), prilocaine (1959), bupivacaine (1957), and etidocaine (1971) have, along with lidocaine, formed the injectable local anesthetic armamentarium for contemporary dental practice. Articaine, an amide local anesthetic containing a thiophene ring was introduced in Europe and Canada during the 1980s.

These agents, either as a plain solution or in combination with a vasoactive substance, usually epinephrine, provide the dentist with a wide range of clinical activity, from short duration of pulpal anesthesia to long duration of pulpal and soft tissue anesthesia.

Current trends in the use of local anesthetics in dentistry indicate that most dentists require three agents in their practice. A short-duration drug is used for the management of most children, geriatric patients (an ever-growing patient population), and for the medically compromised but still treatable individual. A second anesthetic, of intermediate duration, provides pulpal anesthesia for periods of up to 1 hr, the traditional length of most dental appointments for adults. Indeed, it is the agents within this category that are the most used in dentistry. Significantly, in order to provide this duration of anesthesia, virtually all of these agents require the addition of a vasoactive substance, usually epinephrine, to decrease tissue perfusion and to retain the local anesthetic at the site of injection for a greater period of time. Many doctors also require a longer duration local anesthetic. There are two major uses for this group. The first is for procedures requiring pulpal anesthesia in excess of 60 min (eg, crown and bridge). The second, and increasingly more important, is the use of long-duration local anesthetics in the immediate postoperative period to minimize the need for opioid analgesics (and their attendant side effects).

Table 1 lists the currently available local anesthetics in North America by their expected durations of pulpal (deep) anesthesia. Not all of these drugs or drug combinations are available in every country. Interestingly, the use of epinephrine in ever decreasing concentrations appears to be gaining popularity, as witnessed by the recent availability of 2% lidocaine with 1 : 200,000 epinephrine in several European countries. At the same time, however, drug combinations that include ever greater concentrations of vasoactive substances are also appearing, such as Xylonor 2% Special, which contains both 1 : 100,000 epinephrine and 1 : 50,000 norepinephrine. The package insert[6] mentions the "association of epinephrine and norepinephrine confers on this classic formulation the maximum anaesthetic power." It goes on to state "however, it has become evident with time that it would be useful to have an even stronger anaesthetic solution whilst maintaining the safety associated with the name Xylonor—hence, the Xylonor 3% Noradrenaline (3% lidocaine with 1 : 50,000 norepinephrine)." The 3% Xylonor solution is suggested for dental operations that are considered difficult or of long duration.

With the local anesthetic armamentarium currently available, it is possible for the dentist to select the local anesthetic that is most appropriate for the treatment of the patient at each appointment. It must always be remembered that there are a number of factors that influence these expected durations. These factors include the vascularity of the tissue, the proximity to the nerve, infection or inflammation, anatomy, biological variability, and the type of injection administered (eg, supraperiosteal [infiltration] or nerve block).

* The tragedy of cocaine continues today in the form of drug abuse, leading to a terrible addiction to this potentially dangerous drug. One unique method that is used to transport small volumes of cocaine country to country is termed "body packing" in which the "mule" (the person transporting the cocaine) swallows condoms [double-wrapped] filled with pure cocaine. Twenty to 30 condoms are usually swallowed prior to departure to the United States (or wherever their destination lies) and are reclaimed via enemas once safely arrived. Unfortunately, on occasion a condom will leak, leading to a rapid elevation of cocaine blood concentrations and to seizures that usually result in the death of the "mule."

Table 1. Local Anesthetic Preparations

Formulation	*Common Trade Name*
Short duration: 30 minutes pulpal	
2% Lidocaine	Xylocaine
3% Mepivacaine	Carbocaine
4% Prilocaine (infiltration)	Citanest
Intermediate duration: 60 minutes pulpal	
4% Articaine with 1:100,000 epinephrine	Ultracaine Forte
4% Articaine with 1:200,000 epinephrine	Ultracaine
2% Lidocaine with 1:50,000 epinephrine	Xylocaine
2% Lidocaine with 1:100,000 epinephrine	Xylocaine
2% Lidocaine with 1:200,000 epinephrine	
2% Lidocaine with 1:50,000 epinephrine and 1:50,000 norepinephrine	Xylonor 2% Special
3% Lidocaine with 1:50,000 norepinephrine	Xylonor 3% Noradrenaline
2% Mepivacaine with 1:20,000 levonordefrin	Carbocaine
2% Mepivacaine with 1:100,000 epinephrine	Scandonest
4% Prilocaine (nerve block)	Citanest
4% Prilocaine with 1:200,000 epinephrine	Citanest Forte
2% Procaine + 0.4% propoxycaine with 1:20,000 levonordefrin	Ravocaine
Long duration: 90+ minutes pulpal	
0.5% Bupivacaine with 1:200,000 epinephrine	Marcaine
1.5% Etidocaine with 1:200,000 epinephrine	Duranest

The primary factor involved in the selection of a local anesthetic for use will usually be the desired length of pain control. Once a drug is selected, consideration must next be given to the presence of any contraindication to administration of that drug or drug combination. Absolute and relative contraindications to the administration of local anesthetics are listed in Table 2.

The local anesthetics currently available for use in dentistry quite adequately meet the requirements of safety and efficiency desired of all drugs. Indeed there are no drugs used for the management of pain that are as safe or as effective as local anesthetics. Still, in recent years, pharmacologists and anesthesiologists have worked to design new drugs or drug formulations that will aid in achieving ever greater patient comfort and safety.

FUTURE TRENDS IN LOCAL ANESTHETIC DRUGS

Considerable interest has focused upon improvements in injectable drugs to block pain impulses from reaching the brain. Centbucridine, oxethazine, and articaine are but three examples of recently developed local anesthetics that are reported to possess interesting characteristics. Yet another is ropivacaine, an amide local anesthetic receiving considerable scrutiny at this time. Also in the realm of local anesthetic drugs are developments initially employed in medicine but of potential interest in dentistry. One is to increase the ability of the local anesthetic to cross (diffuse) relatively impervious barriers, such as intact skin. EMLA, an acronym for eutectic mixture of local anesthetics has been employed with some success in the operating room as a means of making venipuncture less traumatic. In addition, the ability to speed the onset of anesthesia as well as make the administration of local anesthetics into the skin (or any tissue) more comfortable for the patient has been considered in the recent development of carbonated local anesthetics. As a point of interest, the two biological toxins saxitoxin and tetrodotoxin, which are highly potent, ultralong-acting anesthetics, will also be mentioned.

Ropivacaine

Ropivacaine is a new long-duration amide anesthetic. It is similar structurally to mepivacaine and bupivacaine but differs from them in that it is prepared as an isomer rather than as a racemic mixture. Data indicate that ropivacaine has a greater margin between the convulsive dose and lethal dose than does bupivacaine[7] and also that ropivacaine has a lower arrhythmogenic potential than bupivacaine.[8] The elimination half-life of ropivacaine is 25.9 min, which is considerably shorter than other amides.[9] The primary use of ropivacaine in anesthesiology, to date, has been in regional nerve block. Its potential for use in dentistry awaits clinical evaluation.

Articaine

Articaine, a relatively new (synthesized 1969) amide local anesthetic differs from others in that it contains a sulfur molecule in a thiophene ring. Articaine reportedly possesses several properties that make it highly attractive to clinicians. First, it has an onset of clinical action that is significantly more rapid than other local anesthetics[10]; second, the drug is said to diffuse through both soft and hard

Table 2. Contraindications to Local Anesthetics

Medical Problem	*Drugs to Avoid*	*Type of Contraindication*	*Alternative Drug*
Local anesthetic allergy, documented (e.g., esters)	All local anesthetics in same chemical class	Absolute	Local anesthetics in different chemical class (eg, amides)
Sulfa allergy	Articaine	Absolute	Nonsulfur-containing local anesthetic
Bisulfite allergy	Vasoconstrictor-containing local anesthetics	Absolute	Any local anesthetic without vasoconstrictor
Atypical plasma cholinesterase	Esters	Relative	Amides
Methemoglobinemia, idiopathic or congenital	Articaine, prilocaine	Relative	Other amides or esters
Significant liver dysfunction (ASA III–IV)	Amides	Relative	Amides or esters, but judiciously
Significant renal dysfunction (ASA III–IV)	Amides and esters	Relative	Amides or esters, but judiciously
Beta-adrenergic blockade	Local anesthetics containing vasoactive substances	Relative	Local anesthetics without vasoactive substances
Significant cardiovascular disease (ASA III–IV)	High concentrations of vasoconstrictors (as in racemic epinephrine in gingival retraction cords	Relative	Local anesthetics with epinephrine concentrations of 1:200,000 or 1:100,000, 3% mepivacaine, or 4% prilocaine
Clinical hyperthyroidism: (ASA III–IV)	High concentrations of vasoconstrictors (as in racemic epinephrine in gingival retraction cords)	Relative	Local anesthetics with epinephrine concentrations of 1:200,000 or 1:100,000, 3% mepivacaine or 4% prilocaine

tissues much more effectively than other drugs.[11] This increased diffusibility enables articaine to provide soft and hard tissue anesthesia of the palate without the need for a palatal infiltration of nerve block in a high percentage of cases. Deposition of articaine into the buccal fold (ie, supraperiosteal injection) may provide clinically adequate palatal anesthesia in a high percentage of cases.[12,13] There are two contraindications to use of articaine that must be noted. Methemoglobinemia is seen when high doses (greater than those employed in dentistry) are administered. The use of articaine in patients with histories of acquired or congenital methemoglobinemia is therefore relatively contraindicated. Documented allergy to sulfur represents an absolute contraindication to articaine administration.

Articaine has been available in dental cartridges throughout Europe and Canada since the mid-1980s. The popularity of articaine where it is available serves as an indicator as to the efficacy of the drug.

Centbucridine

Centbucridine, a quinoline derivative, is five to eight times as potent as lidocaine, with an equally rapid onset of action and an equivalent duration of action. Significantly, centbucridine does not effect the central nervous or cardiovascular systems adversely except when administered in very large doses.[14] Most of the clinical work on centbucridine has been published in Indian medical journals. Centbucridine has been used in subarachnoid and extradural anesthesia[15] and in intravenous regional anesthesia.[16] Vacharajani et al[17] compared the efficacy of 0.5% centbucridine to 2.0% lidocaine for dental extractions in 120 patients. They reported that the degree of analgesia attained with centbucridine compared well to that obtained with lidocaine. Centbucridine was well tolerated, with no significant changes in cardiovascular parameters and no serious side effects. More research is required into centbucridine to determine its ultimate standing in the dental local anesthetic armamentarium.

Oxethazaine

The clinical use of oxethazaine was reported in 1990 by Brennan and Langdon.[18] Oxethazaine is claimed to be 2,000 times as potent as lidocaine and 500 times as potent as cocaine. It is currently used as an antacid preparation for the topical relief of pain in conditions such as hiatal

hernia, where the local pH is very low. Since oxethazaine is active in an acid environment, it might prove to be an effective anesthetic in areas of acute periapical pathology. Used in a concentration of 0.1% at a pH of 3, oxethazaine was found to be an effective anesthetic in all 20 patients requiring minor oral surgical procedures. In two patients with acute periapical pathology, 0.1% oxethazaine was clinically effective after failure of 2% lidocaine with 1 : 80,000 epinephrine. The duration of anesthesia was found to be similar to that of 2% lidocaine with 1 : 80,000 epinephrine.

EMLA

The eutectic mixture of local anesthetics (EMLA), is used topically in place of lidocaine or benzocaine sprays, gels, or creams. The latter are only effective in penetrating mucosal membranes or damaged skin; they are ineffective on intact skin. The development of an oil and water emulsion containing high concentrations of lidocaine and prilocaine in the base form resulted in EMLA, a cream that provides cutaneous local anesthesia.[19–20] The local anesthetic base is dissolved in oil, and an emulsion is formed with an aqueous vehicle system. The concentration of lidocaine in such a formulation can reach up to 20% in the emulsion droplets. If both lidocaine and prilocaine are combined in crystal form, they produce a eutectic mixture that can achieve a concentration of about 80%.[19] EMLA is a very important breakthrough. A 5% EMLA cream will penetrate intact skin. Use of 5% EMLA significantly reduced pain of intravenous needle insertion compared with a placebo cream without producing any significant epithelial irritation.[21] Additionally, the potential for toxic blood concentrations developing with EMLA is quite remote—the peak plasma anesthetic concentrations occur 180 min after application.[22] EMLA appears most appealing for use in pediatric populations in whom fear of needle insertion is rampant. The only drawback to EMLA is the necessity of applying EMLA over the selected site for needle penetration 45 to 60 min before the procedure.[23] The utility of EMLA intraorally is doubtful, although Holst and Evers[24] demonstrated that EMLA can block the pain of needle insertion through oral mucosa. The absence of a cutaneous layer in the mouth makes traditional topical anesthetic formulations quite effective.

Carbonated Local Anesthetics

Carbonated local anesthetics are not really new, their use being described as early as 1965.[25] However, there has been a recent resurgence of interest. Use of carbonated local anesthetics provides two advantages: a more rapid onset of anesthesia and a more comfortable injection. Carbon dioxide enhances diffusion of the local anesthetic through nerve membranes and thus produces a more rapid onset of nerve block. As carbon dioxide diffuses through the nerve membrane, the intracellular pH is decreased, resulting in an increased intracellular concentration of charged cations, the primary active form of the drug. As the cation form of the drug will not readily diffuse out of the nerve, a longer duration of anesthesia is also noted. The problem clinically has been that if the carbonated local anesthetic agent is not injected almost immediately after opening the vial, the carbon dioxide gas diffuses out of solution, significantly diminishing its effectiveness. The anesthetic drug must be administered within a very short period of time after preparing the syringe. Another approach has been the addition of sodium bicarbonate immediately prior to anesthetic administration. This increases the pH of the solution, increasing the number of uncharged base molecules in solution. This formulation of lidocaine with epinephrine plus sodium bicarbonate (pH 7.20) provides a more rapid onset of anesthetic block[26] (2 min) than commercially prepared lidocaine plus epinephrine (pH 4.55, 5 min onset). The sodium bicarbonate formulation appears to be more practical clinically than the carbon dioxide procedure. However, if the pH of the anesthetic solution is too high, the local anesthetic will precipitate out of solution as the drug base.

Biotoxins

Tetrodotoxin (TTX) and saxitoxin (STX) are classified as biologic toxins (biotoxins). Found in the puffer fish (TTX) and certain species of dinoflagellates (STX), they specifically block sodium channels on nerve membranes when applied to their outer surfaces and thus produce conduction blockade. Although these agents are about 250,000 times as potent as procaine for conduction blockade in isolated nerve preparations,[27] they are both highly toxic and will not pass readily through the epineurium surrounding peripheral nerves. They therefore provide little or no conduction blockade in sciatic nerve blocks.[28] However, when administered via subarachnoid block in sheep, the duration of spinal anesthesia is almost 24 hr.[28] Unfortunately, both TTX and SSX are extremely difficult to synthesize and are not very stable in aqueous solutions, thereby significantly limiting their usefulness. There is little likelihood of these agents being of any clinical value in dentistry in the near future.

FUTURE TRENDS IN PAIN CONTROL

The contemporary dental practitioner has available a wide variety of drugs, equipment, and techniques with which to provide safe and effective pain control through local anesthesia. However, there still remain patients for whom local anesthetics are ineffective, contraindicated, or who

simply cannot psychologically tolerate intraoral injections. For these patients the introduction of alternative techniques of pain control holds great promise.

Phonophoresis and electronic dental anesthesia are two pain control techniques that do not require the injection of drugs into tissues. Phonephoresis, the use of high frequency (1.000,000 Hz) sound waves[29] to drive drugs into tissues through intact skin or mucous membranes has been used primarily in orthopedic and sports medicine. Cortisone and lidocaine can be deposited to a depth of approximately 5 cm into the knee joint without injection with phonophoresis. Conceptually, phonophoresis should be of great value in dentistry where fear of injection is great. Considerable research is still necessary, however, before phonophoresis becomes clinically acceptable.

Electronic dental anesthesia (EDA) is the dental modification of TENS (transcutaneous electrical nerve stimulation), a technique used in medicine for the management of chronic pain, and ever increasingly in sports medicine in the treatment of injuries. EDA is useful in dentistry for the management of both chronic and acute pain, as an effective alternative to injectable local anesthetics. Success rates with EDA have been demonstrated to be approximately 85% in nonsurgical periodontal procedures,[30] 78% to 80% in restorative dentistry,[30,31] and 75% in crown and bridge.[30] Quarnstrom has demonstrated that the use of inhalation sedation with nitrous oxide and oxygen can increase the efficacy of EDA by approximately 10% to 15%.[32] The use of battery-operated EDA devices that provide high frequency electrical stimulation of either 120 Hz or 16,000 Hz to the treatment area enables the needle-phobic patient to comfortably receive dental care without the requirement of local anesthetic injection.

SUMMARY

Although the current armamentarium of available local anesthetic solutions is adequate to meet the needs of virtually all patients and all procedures, research continues on newer agents that may prove to be clinically superior. Longer acting, faster acting, more comfortable, and even safer local anesthetics may be just beyond the horizon.

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