FEATURE

Non Injectable Local Anesthesia (NILA) for Periodontal Debridement: A Review and Discussion for Subgingival Application

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(Part 1 of a 2 part series)

Introduction

Figure 1

Oral health professionals have long used local anesthetic in conjunction with non surgical periodontal debridement with an objective to achieve maximum clinical outcomes while providing optimal patient comfort. For decades, clinicians have been using either injectable or topical anesthesia when pain control is needed for scaling and root planing procedures. The use of "topicals" in this instance has been especially alluring as the needle free anesthesia without the classic numbing effects of injectable anesthesia is extremely desirable for the clinician and the patient.[1,2] However, the traditional topical application of local anesthetics often fails to provide the effect needed to carry out debridement procedures comfortably. To improve clinical effectiveness, manufacturers have recently expanded the delivery methods of local anesthetics beyond traditional topical and injectable applications. Clinicians now have options to choose products that allow for the placement of local anesthesia drugs directly into periodontal pockets. In these instances, a blunt tipped canula, not a needle, is indicated as the "non injectable" local anesthetic is placed in a sulcus or pocket to be systemically absorbed. (See Figure 1). With the abundance of product choices now available, it is important for practitioners to have an up to date understanding of non injectable local anesthetics (NILA) for maximum effectiveness and safety. This article, presented as a two part continuum, will examine the classifications, formulations, maximum recommended dosage (MRD) and dosage control of NILA. It will also explore considerations specific to subgingival application.

Local Anesthesia in Dentistry today

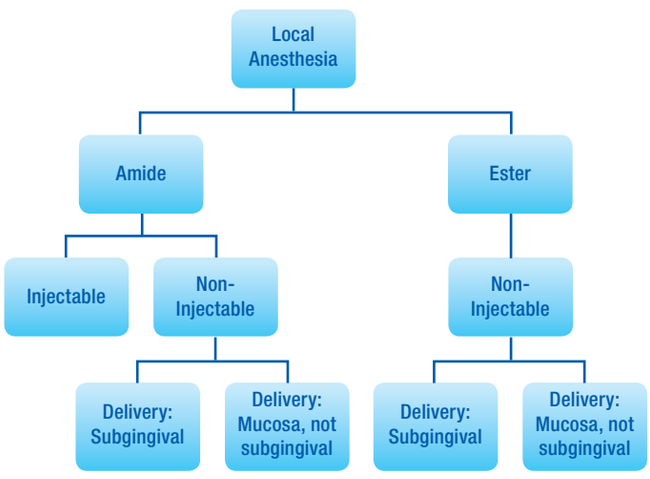

Figure 2

Classifications and Formulations

In dentistry, local anesthesia is classified as either ester type or amide type compounds. Today, all injectable anesthetics, available in cartridge form, are amides.[3] Those not for injection, are available in amides or esters and depending on the manufacturer and application methods that include traditional mucosal delivery (non subgingival) or subgingival delivery. (See figure 2).

Esters

Figure 3

For intraoral use, benzocaine and tetracaine are the most common compounds found within the ester classification. Products can be purchased in various formulations including gels, liquids, sprays, creams, ointments and patches. Familiar brand names include Hurricane, Cetacaine, Ultracare and Topex. Practitioners should consult each manufacturer to determine if traditional supragingival "topical" applications or non injectable subgingival applications are available. (See figure 3).

Benzocaine has effective concentrations in dentistry at 6–20%. A 2% concentration is recommended for topical applications of tetracaine. Tetracaine is the most potent, not for injection, dental anesthesia; excessive doses and too frequent administration should be avoided. Tetracaine is typically used in combination with other drugs; some products include combinations of two or more drugs as this can provide a much more useful range of anesthesia to any of the individual drugs acting alone.[3]

Cetacaine (Cetylite Industries Inc.) and Hurricane (Beutlich Pharmceuticals LLC) are available as a traditional topical local anesthetic and for subgingival placement. Cetacaine is an example of a combination ester type and contains 14% benzocaine, 2% tetracaine and 2% butamben. According to the product insert, Cetacaine is "a topical anesthetic indicated for the production of anesthesia of all accessible mucous membrane except the eyes." Although the product is not specifically indicated for application in periodontal pockets during periodontal debridement, with the Cetacaine liquid kit, the manufacturer provides armamentarium and instructions for subgingival delivery and indicates that the maximum dose when using the syringe provided is 0.4 ml per office visit.[4] Recently, from the makers of Hurricane, HurriPak has become available in Canada. Hurripak is a liquid containing 20% benzocaine; it comes in a jar and is packaged with disposable syringes and plastic tips that allow placement of the liquid into the periodontal pocket. The maximum recommended dose of HurriPak is 3 ml.[5]

Amides

For those preferring amide type compounds, lidocaine or lidocaine and prilocaine, eutectic mixtures are available. Effective concentrations in dentistry are 2–5%. As with the esters, the purpose of the combination of drugs is to enhance clinical effectiveness. Amide products for intraoral use can be purchased in ointments, sprays, gels, liquids and liquid gel—liquid at room temperature, gel at body temperature. (See figure 4.)

Figure 4

For practitioners wanting an amide packaged with armamentarium for subgingival application, choice is more limited than within the ester classification. Available in Canada since 2010, and specialized for subgingival application is Oraqix (DENTSPLY Pharmaceutical), a thermosetting liquid gel containing 2.5% prilocaine and 2.5% lidocaine that is packaged in a 1.8 g cartridge. In addition to providing excellent tissue anesthesia and occasional pulpal anesthesia, this system has wide margins of safety, a known maximum safe dose and easily quantified volumes dispensed due to its packaging in cartridge form.[3] According to the product monograph MRD of Oraqix is 5 cartridges.[9] With the exception of Oraqix, all NILA products used intraorally— including those that are packaged with armamentarium for subgingival application—carry indications for general use on all accessible mucous membrane. Oraqix is indicated specifically for application in periodontal pockets for moderate pain during scaling and/or root planing[9] and has received Health Canada approval for this indication.

Adverse Effects

Adverse effects may result from hypersensitivity or allergy. Esters are associated with a higher incidence of allergic reactions but allergies to amides have been described as virtually unknown.[7] More often, adverse effects are dose related, caused by excessive dosage or rapid absorption of the drug. Products void of an exact indication for use in periodontal pockets may require greater deliberation to ensure maximum effectiveness and safe practice.

The next article in this series will cover adverse effects in more detail as it examines maximum recommended dosage (MRD), dosage control and considerations specific to the subgingival application of NILA.

References

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3. *Bassett KB, DiMarco AC, Naughton DK. Local anesthesia for dental professionals. Pearson. New Jersey. 2010.*
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5. *Beutlich Pharmaceuticals HurriPak Drug Facts.. Waukegan, Illinois. Date of publication unknown. Source: www.beutlich.com/documents/hurripak/hurripak_drug_facts*
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oraqix®

(lidocaine and prilocaine
periodontal gel) 2.5% / 2.5%

Prescribing Summary

Patient Selection Criteria

Product mongraph PART I: Health Professional Information
SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Topical Periodontal Administration DO NOT INJECT	Gel / Lidocaine 25 mg/mL; Prilocaine 25 mg/mL	Hydrochloric Acid, NF, Ph Eur Poloxamer 188, purified Poloxamer 407, purified Purified Water, USP, Ph Eur

INDICATIONS AND CLINICAL USE

Adults

ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) is indicated for topical application in periodontal pockets for moderate pain during scaling and/or root planing.

ORAQIX® should NOT be injected.

Geriatrics (> 65 years of age): There are limited data available on the use of ORAQIX® in the elderly. Greater sensitivity of some older individuals cannot be ruled out. Caution is advised in dose selection for the elderly (see WARNINGS and PRECAUTIONS, Special Populations, Geriatrics).

Pediatrics (< 18 years of age): ORAQIX® is not recommended to be used in children (see WARNINGS and PRECAUTIONS, Special Populations, Pediatrics).

CONTRAINDICATIONS

ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) is contraindicated:

- in patients with a known history of hypersensitivity to local anesthetics of the amide type or to any other component of the product;
- in patients with congenital or idiopathic methemoglobinemia

Safety Information

WARNINGS AND PRECAUTIONS

ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) must not be injected.

ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) should not be used with standard dental syringes.

General

Allergy: Allergic and anaphylactic reactions associated with lidocaine or prilocaine can occur. These reactions may be characterized by urticaria, angioedema, bronchospasm, and shock. If these reactions occur they should be managed according to standard clinical practice.

Methemoglobinemia: Prilocaine can cause elevated methemoglobin levels particularly in conjunction with methemoglobin inducing agents. Methemoglobinemia has also been associated with amino- or nitro-derivatives of benzene e.g. aniline, dapsone and lidocaine although reports on the link between lidocaine treatment and methemoglobinemia are limited. Methemoglobinemia is well documented in relation to prilocaine and lidocaine combination treatment and correlated with exposure to prilocaine and the plasma levels of its metabolite *o*-toluidine.

Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) should not be used in those patients with congenital or idiopathic methemoglobinemia.

Patients taking drugs associated with drug-induced methemoglobinemia are also at greater risk for developing methemoglobinemia. Treatment with ORAQIX® should be avoided in patients with any of the above conditions or with a previous history of problems in connection with prilocaine treatment (see DRUG INTERACTIONS, Methemoglobinemia).

The development of methemoglobinemia is generally dose-related. Levels of methemoglobin observed after application of the ORAQIX® in clinical trials did not exceed normal values (i.e. <2% of the individual patient's total hemoglobin). The individual maximum level of methemoglobin in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5 g ORAQIX® (see OVERDOSAGE, Methemoglobinemia).

Ear/Nose/Throat

ORAQIX® should not be used in clinical situations where it can penetrate or migrate into the middle ear. Tests on laboratory animals (guinea pigs) have shown that a cream formulation containing lidocaine and prilocaine has an ototoxic effect.

When the same animals were exposed to the cream formulation in the external auditory canal, no abnormalities were observed. Minor structural damage to the tympanic membrane in guinea pigs was observed when a lidocaine-prilocaine cream formulation was applied directly to the membrane.

Care should be taken to avoid excess ORAQIX® from spreading to the oropharyngeal mucosa.

Special Populations

Pregnant Women: ORAQIX® should be used during pregnancy only if the benefits outweigh the risks. There are no adequate and well-controlled studies to evaluate ORAQIX® during pregnancy. Animal reproduction studies are not always predictive of human response.

Lidocaine and prilocaine cross the placental barrier and may be absorbed by the fetal tissues. It is reasonable to assume that lidocaine and prilocaine have been used in a large number of pregnant women and women of child-bearing age. No specific disturbances to the reproductive process have so far been reported, e.g., an increased incidence of malformations or other directly or indirectly harmful effects on the fetus. However, care should be given during early pregnancy when maximum organogenesis takes place.

Nursing Women: Lidocaine and, possibly, prilocaine are excreted in breast milk, but in such small quantities that there is generally no risk to the infant being affected at therapeutic dose levels due to low systemic absorption.

Pediatrics (<18 years of age)
Safety and effectiveness in pediatric patients have not been studied. Very young children are more susceptible to methemoglobinemia associated with prilocaine treatment and this is related to the development of the enzyme methemoglobin reductase which converts methemoglobin back to hemoglobin. Methemoglobin reductase reaches adult levels at between 3 and 6 months.

Geriatrics (> 65 years of age): Of the total number of subjects in clinical studies of ORAQIX®, 7% were aged 65 and over, while 1% were aged 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The clinical safety database included 559 subjects, 391 of whom were exposed to ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) and 168 to placebo gel. In a crossover study, 170 patients exposed to ORAQIX® also received an injection of 2% lidocaine with epinephrine.

The most frequent adverse reactions in clinical trials were local reactions in the oral cavity. The frequency and type of reactions were similar for ORAQIX® and placebo-treatment patients.

The treatment-emergent adverse events observed in three placebo-controlled parallel studies (B1 – B3) are summarized in Table 1.

Table 1: Treatment-Emergent Adverse Events for ORAQIX® in placebo controlled parallel studies (B1 – B3) (≥ 1% and more frequent than placebo)

Adverse Event	ORAQIX® n = 169 (case, %)	Placebo n = 168 (case, %)
Application Site Reaction	25 (15)	20 (12)
Headache	4 (2)	3 (2)
Taste Perversion	4 (2)	1 (1)
Accident and/or Injury	2 (1)	2 (1)
Application Site Edema	2 (1)	1 (1)
Respiratory Infection	2 (1)	0 (0)

Allergic Reactions: In rare cases, local anesthetics have been associated with allergic reactions and in the most severe instances, anaphylactic shock (see WARNINGS AND PRECAUTIONS, Sensitivity, Allergy) Allergic reactions were not reported during clinical studies with ORAQIX®. Very rare cases of anaphylactic or anaphylactoid reactions associated with the use of ORAQIX® have been reported.

For more details on adverse events reported during clinical trials, see ADVERSE REACTIONS in the Supplemental Product Information.

To report a suspected adverse reaction, please contact DENTSPLY Canada Inc. by:
Toll-Free Number: (800) 263-1437
Fax: (905) 851-9809
By regular mail: DENTSPLY Canada Inc.: 161 Vinyl Court, Woodbridge,

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations

ORAQIX® is for TOPICAL USE ONLY. DO NOT INJECT. ORAQIX® should not be used with standard dental anesthetic syringes. Only use this product with the ORAQIX® Dispenser, which is available from DENTSPLY Canada.

Conditions where dosing may require adjustment:

- In patients who are administered other local anesthetics or amide type local anesthetics (see DRUG INTERACTIONS).
- In elderly patients or those with impaired elimination, dose selection should be cautious, usually starting at the low end of the dosing range to avoid toxicity due to increased blood levels of lidocaine and prilocaine.

Recommended Dose

Typically, one cartridge (1.7 g) or less of ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) will be sufficient for one quadrant of the dentition. The maximum recommended dose of ORAQIX® at one treatment session is five cartridges, i.e. 8.5 g gel containing 212.5 mg lidocaine base and 212.5 mg prilocaine base.

If additional local anesthesia is needed in combination with ORAQIX®, please refer to the product monograph of each adjunctive anesthetic. Because the systemic toxic effects of local anesthetics are additive, it is not recommended to give any further local anesthetics during the same treatment session, if the amount of ORAQIX® administered corresponds to the maximum recommended dose of five cartridges.

The use of ORAQIX® in children and adolescents has not been assessed and therefore its use is not recommended in patients less than 18 years old.

Administration

Apply ORAQIX® on the gingival margin around the selected teeth using the blunt-tipped applicator included in the package, then fill the periodontal pockets with ORAQIX® using the blunt-tipped applicator until the gel becomes visible at the gingival margin.
Wait for 30 seconds before starting treatment. A longer waiting time does not enhance the anesthesia. Anesthetic effect, as assessed by probing of pocket depths, has a duration of approximately 20 minutes (individual overall range 14 - 27 minutes). If the anesthesia starts to wear off, ORAQIX® may be re-applied if needed.

At room temperature ORAQIX® stays liquid; it turns into an elastic gel at body temperature. If it becomes excessively viscous in the cartridge, the cartridge should be placed in a refrigerator until it becomes a liquid again. When in the liquid state, the air bubble visible in the cartridge will move if the cartridge is tilted.

Instructions for application of ORAQIX® using the ORAQIX® Dispenser are provided in the package insert supplied with the ORAQIX® Dispenser.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

STORAGE AND STABILITY

ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) is a liquid at room temperature and transforms to an elastic gel at body temperature in the periodontal pockets.

Store at room temperature 15° - 30°C.

SPECIAL HANDLING INSTRUCTIONS

DO NOT FREEZE. Some components of ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) may precipitate if cartridges are frozen. Cartridges should not be used if they contain a precipitate.

Do not use dental cartridge warmers with ORAQIX®. The heat will cause the product to gel.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ORAQIX® (Lidocaine and Prilocaine Periodontal Gel) is a microemulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine base in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature, therefore both local anesthetics exist as liquid oils rather than as crystals. ORAQIX® contains poloxamer excipients, which show reversible temperature-dependent gelation. Together with the lidocaine-prilocaine 1:1 mixture, the poloxamers form a low-viscosity fluid system at room temperature and an elastic gel in the periodontal pocket. ORAQIX® is administered into periodontal pockets, by means of the supplied special applicator. Gelation occurs at body temperature, followed by release of the local anesthetics, lidocaine and prilocaine.

ORAQIX® is supplied in single-use glass dental cartridges that provide 1.7 g gel (42.5 mg of lidocaine and 42.5 mg of prilocaine). Each gram of ORAQIX® contains 25 mg lidocaine base and 25 mg prilocaine base. The gel also contains poloxamer 188 purified, poloxamer 407 purified, hydrochloric acid, and purified water. The pH of ORAQIX® is 7.5-8.0.

Individually blister-packaged cartridges of ORAQIX® are distributed in a carton of 20. Each individual blister package also contains a sterile blunt-tipped applicator. The applicator has a blunt-tip end for ORAQIX® application and a sharp-tip end for piercing the rubber

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