An Observation on the Superiority of Articaine versus Lidocaine in Dental Anesthesia

Abstract

This course is designed to educate the dental-health professional regarding the potential superiority of articaine 4 percent in relation to lidocaine 2 percent in dental anesthesia. It is also intended to illustrate the differences between these products regarding their chemistry, pharmacology, metabolism and use.

Educational objectives

Upon completion of this course the dental health professional will be able to:

- Appreciate the history of these compounds’ development in dental anesthesia.
- Gain insight into the safety and efficacy of articaine and lidocaine.
- Understand, in detail, articaine and lidocaine’s main characteristics when used in the clinic.
- Consider the best choice of anesthetic for complicated dental procedures.
- Understand the use of articaine and lidocaine in children and geriatric patients.

Introduction

This CE course is an illustration of articles and some scientific studies that have come into the dental anesthetics debate from 2011 through 2015. It is mainly a discussion of the comparison of articaine 4 percent to lidocaine 2 percent regarding both drugs’ safety and efficacy.

In a 2011 article entitled, “Articaine: Review of the Literature,” 1 published in the British Dental Journal, the authors do a more than adequate job of looking at articaine as a new local anesthetic (LA) entering the market.

The literature contains numerous comparisons establishing the efficacy of articaine when compared predominantly to lidocaine, but also with other anesthetics.

Controlled clinical studies and other retrospective studies point out the added enhanced effect of using articaine alongside lidocaine in certain procedures, such as intraosseous anesthesia in patients with irreversible pulpitis. 2

Several more recent articles 3,4 discuss trials that also confirm the efficacy of articaine versus lidocaine in irreversible pulpitis.
Chemistry and pharmacology

Articaine and lidocaine have very different chemical structures, chemistries and pharmacology. Articaine differs from lidocaine in that its chemical structure contains a thiophene ring instead of a benzene ring configuration. The thiophene ring allows articaine a greater lipid solubility and potency in the administered dose.

Protein binding differs slightly between articaine and lidocaine (about 74 percent at pH 8.3 and about 75 percent at pH 8.5). The high level of binding affects the duration of action. Highly bound agents are not re-absorbed into the central circulation as quickly and may be less prone to systemic toxicity.5

The dissociation constant (pKa) affects the onset of action. A lower pKa means that more uncharged base molecules are present to diffuse through the nerve sheath, and thus the onset time is decreased. Articaine has a lower pKa than lidocaine.

The two drugs’ metabolism is also different. As for articaine’s metabolism, a small amount (10 percent) is handled by the liver, but about 90 percent is hydrolyzed in the serum by nonspecific blood esterases.6

In contrast, lidocaine is predominantly metabolized in the liver (70 percent) in a relatively slow manner, thereby causing concentrations of the metabolite xylidide, in its own right an anesthetic, to remain in circulation, potentially offering some safety hazard.

Since articaine produces an equal if not better anesthetic effect, this offers the advantage of using it in a larger concentration than some other LA’s with a reduced risk of systemic toxicity.

The elimination of articaine is exponential, with a half-life of 20 minutes. Since articaine is hydrolyzed in the serum, the risk of systemic intoxication is expected to be lower than with other anesthetics, especially if repeated injection is performed.

Efficacy

In a previously mentioned article, the authors use 116 articles published before 2011 to put articaine in perspective between other LA’s. There are numerous comparisons establishing the efficacy of articaine when compared predominantly to lidocaine, but also with other anesthetics. They use controlled clinical trial studies rather than retrospective or anecdotal data for comparison. Several studies point out the added enhanced effect of using articaine alongside lidocaine in certain procedures, such as intraosseous anesthesia in patients with irreversible pulpitis.2

Several more recent articles discuss trials that also confirm the efficacy of articaine versus lidocaine in irreversible pulpitis.3,4

A recent meta-analysis published by Kung, McDonagh and Sedgley in August 2015 showed superiority of articaine over lidocaine in patients with symptomatic irreversible pulpitis.7

Two hundred and seventy-five studies were identified from a search of four substantive databases using a strict inclusion/exclusion protocol. In addition, in combined studies, articaine was more likely than lidocaine to achieve successful anesthesia. For combined mandibular anesthesia studies, articaine was superior to lidocaine. There were no reports of adverse events.

Multiple controlled clinical trials have established the efficacy of articaine in local anesthesia. Most of these studies were conducted using lidocaine as the comparator drug.8 More recent studies have shown some advantages of articaine versus lidocaine. Hassan and others9 conducted a study in 20 patients needing bilateral extraction of maxillary premolars for orthodontic purposes. Articaine showed statistically significant differences in several areas including perception of pain, onset of action and duration of anesthesia. The use of articaine was said to eliminate the need for palatal injection that can be painful.

Several meta-analyses have been conducted by Katyal10 and most recently, Brandt and others.1 Both suggest equal efficacy of articaine, but in the Brandt analysis, articaine showed a statistically higher probability of anesthetic success superior to lidocaine in both infiltration and mandibular block. There was no significant difference in only symptomatic teeth.

Chemical components and differentiation

Commercially available articaine and lidocaine differ in chemical components that impact preservation of the vaso-constrictor and excipients.

The sodium chloride content is much lower in articaine than in lidocaine. Sodium chloride is used to make the solutions for injection isotonic which helps to minimize the pain on injection. Articaine requires 1mg/mL of sodium chloride, while lidocaine uses 6.5mg/

<table>
<thead>
<tr>
<th>Parameter/substance</th>
<th>Articaine</th>
<th>Lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name</td>
<td>3-N-propylamino-propionyl-amino-2-carbomethoxy-4-methylthiophene hydrochloride</td>
<td>2-Diethylamino-2,6-acetoxylidide</td>
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<td>Structural formula</td>
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<td><img src="image2.png" alt="Lidocaine Structural Formula" /></td>
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<tr>
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<tr>
<td>pKa</td>
<td>7.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Partition coefficient</td>
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<tr>
<td>Lipid solubility</td>
<td>1.5</td>
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<tr>
<td>Plasma protein binding</td>
<td>76% (pH 8.5)</td>
<td>74% (pH 8.5)</td>
</tr>
<tr>
<td></td>
<td>54% (pH 7.5)</td>
<td>61% (pH 7.5)</td>
</tr>
</tbody>
</table>

Table 1: Basic physical/chemical properties of articaine and lidocaine
mL for isotonicity. The osmolarities of the two products are very similar, about 270-290 mOsm (micro-osmoles).

This brings them into the range of a 0.9 percent sodium chloride solution (~280 mOsm), which is empirically defined as isotonic. Generally a lower LA concentration requires more sodium chloride to make the solution for injection isotonic.

Epinephrine is a readily oxidizable substance and requires the presence of an antioxidant to prevent degradation during the manufacturing process and shelf life. It is not important if the sodium or potassium salt of the antioxidant is used. Hence, either sodium metabisulphite or potassium bisulphite is suitable as an antioxidant.

Articaine uses the sodium salt (sodium metabisulphite about 0.50 mg/ml), while some lidocaines use the potassium salt (potassium metabisulphite about 1.2mg/ml).12 In most instances the concentration of metabisulphite used in lidocaines is more than double that used in articaine-based dental anesthetics. This is possibly due to the fact that most lidocaine-based formulations have been developed some time ago when overages of epinephrine up to 20 percent were permitted. Today the maximum permitted overage of epinephrine is 15 percent (see USP Compendia formulations).

Sodium edetate (EDTA) was commonly used in LAs formulated in the 70s and 80s when high-quality polished stainless steel (e.g., SS 316L) was not available for drug-preparation tanks. Articaine does not contain EDTA.

Many lidocaine products still use EDTA (0.25mg/ml).11 There is some potential for EDTA-related allergic reactions, but the incidence is low. More important EDTA is not an essential excipient for the formulation of dental anesthetics, and should be avoided.

Safety

Controversy still swirls around articaine and the incidence of neurotoxic effects, particularly paresthesia.

An article by Haas and Lennon published in 1995 seems to be the original source for this controversy.12 This paper analyzed 143 cases reported to the Royal College of Dental Surgeons of Ontario over a 21-year period.

The results from their analysis seemed to indicate that 4 percent anesthetics had a higher incidence of causing paresthesia. The authors concluded that “…the overall incidence of paresthesia following local anesthesia administration for nonsurgical procedures in dentistry in Ontario is very low, with only 14 cases being reported out of an estimated 11,000,000 injections in 1993. However, if paresthesia does occur, the results of this study are consistent with the suggestion that it is significantly more likely to do so if either articaine or prilocaine is used.”

An interesting finding in the Haas and Lennon analysis is the different frequency between paresthesia of the lingual nerve and the inferior alveolar nerve (IAN). The lingual nerve (tongue) is approximately twice as often involved as the inferior alveolar nerve.

The reason for this finding might be that, in performing IAN injections, some practitioners change the direction of the needle at the approximate depth of the lingual nerve. The sharp needle tip may lacerate the nerve or artery on the initial or subsequent path.

Another possible explanation might be that during a subsequent injection for the IAN block, the needle might traumatize the more superficial lingual nerve but without the “electric shock” sensation because the nerve is usually anesthetized on the initial attempt. The cause of the paresthesia may also be a combination of neurotoxicity of the local anesthetic and trauma to the nerve. Nonetheless, direct damage to the nerve caused by 4 percent drugs has never been scientifically proven.13

Only a single controlled clinical study by Malamed, Gagnon and Leblanc has compared articaine to lidocaine in regard to safety and efficacy, particularly paresthesia.14

Published in JADA in February of 2001, this study reported on three identical single-dose, randomized, double-blind, parallel-group, active controlled multicenter studies comparing articaine 4 percent with epinephrine 1:100,000 with lidocaine 2 percent with epinephrine 1:100,000.

A total of 1,325 patients participated in these studies, 882 of which received articaine and 443 who were given lidocaine. The overall incidence of side effects was 22 percent for articaine and 20 percent for the lidocaine group.

The most frequently reported adverse events in the articaine group, excluding post-procedural dental pain, were headache (4 percent), facial edema, infection gingivitis and paresthesia (1 percent). The incidence of these events was similar to that reported for subjects given lidocaine.

Most of the information characterizing articaine as more likely to produce neurotoxicity was gathered retrospectively and biased in patient recruitment. No formal studies have been conducted since Malamed, but Geffen and Haas suggest that “...it would take an unrealistically large trial or cohort to detect statistically significant difference for an event as rare as non-surgical paresthesia.”

Significant literature documentation supports the notion that paresthesia or neurotoxicity in general may be more likely the result of procedural trauma rather than inherent use of LA’s. A review of clinical, anecdotal and post marketing reports conducted by Toma and others and published in 2015 seems to support the theory that procedural trauma could be the principal underlying cause of paresthesia.

Use in special populations (pediatric and geriatric)

There is little evidence in the clinical literature that supports the use of articaine in children under 4 years of age. However, anecdotal information and a report by Brickhouse and others in 2008 suggest that a quarter of dentists surveyed (n=373) used articaine regularly in children aged 2-3 years with no problems.

Lidocaine’s prescribing information gives dosing directions for children 3 years of age and older. Dosages of articaine for children 4 years and older is based on the same maximum dose for adults (7mg/kg).10 According to Yapp, articaine’s use is safe and effective for clinical procedures in children of all ages.
In most cases, the usual precautions for administration of LA's to geriatric patients should be considered, i.e., increase in body mass, decrease in lean body mass, changes in hepatic metabolism, renal elimination, etc. This holds true for both articaine and lidocaine but their differences in metabolism—i.e., serum hydrolysis versus hepatic elimination, respectively—should be considered when gauging the dose.

Manufacturing processes

The type of manufacturing used can have a significant impact on the drug product produced. For dental anesthetics containing epinephrine, there are two acceptable methods of manufacturing: terminal sterilization manufacturing and aseptic manufacturing.

The terminal sterilization process uses heat to sterilize the LA in the filled cartridges and the aseptic process in which the solution for injection is sterilized by passing through sterilizing filters of 0.2 microns. The primary packaging components (glass cartridge, plunger and cap seal) are sterilized separately and components and solution assembled in a sterile environment. Consequently, with aseptic manufacturing, the drug product is not subjected to heat treatment.

Today there is no law that tells us which manufacturing process to use, and generally, drug products that contain heat-sensitive components—for example, epinephrine, polypeptides and biotech drug products—are manufactured via an aseptic process.

Commercial LA's containing epinephrine are manufactured by both methods, since there is considerable heat sensitivity of epinephrine and metabolisphite. Today in the U.S., only one articaine product uses aseptic manufacturing (Orabloc, articaine 4 percent w/epinephrine, marketed by Pierrel Pharma) and in Europe, Ultracaine from Sanofi Aventis, while all other LA's, including lidocaine, use terminal sterilization.

However, it is worth remembering that a few years ago, when Xylocaine was manufactured by the originator, Astra AB, it was manufactured aseptically. One evident advantage of aseptic sterilization vs. terminal sterilization is an increase of six months in shelf life (24 months vs. 18 months).¹⁰

Historic and economic factors

Lidocaine has been a standard of dental anesthesia for more than 60 years. First synthesized under the name Xylocaine (Astra AB), it has remained a staple of dental LA’s. Articaine was introduced as carticaine in Germany in 1976 (Hoechst), the United Kingdom in 1998, the U.S. in 2000 and in Australia in 2005.¹

Articaine formulation containing epinephrine 1:200,000 was only introduced in the U.S. in 2005. In addition, articaine is widely available in Europe under various names, including Orabloc, Septocaine, Ultracaine and others.

European dentists were quick to adopt articaine because of its quick onset time, profound anesthesia and long duration. North America has been slower, since many dentists were trained to use lidocaine as their primary LA. Articaine was made available only in 2000 and 2005, whereas lidocaine has been available since the late 70s.

In dentistry, articaine is used both for infiltration and block injections, with the block technique yielding the greatest duration of anesthesia. In people with hypokalemic sensory overstimulation, lidocaine is not very effective, but articaine works well.

The onset and duration of articaine 4 percent may suggest that half as much anesthetic need be used in patients in comparison with lidocaine 2 percent, which sometimes may require multiple re-injections to establish adequate anesthesia.

Summary

Articaine is an amide anesthetic that is as effective as—or more effective than—lidocaine in dental procedures. Articaine is unique because it contains an additional ester group that is metabolized by esterases in blood and tissue.

The elimination of articaine is exponential with a half-life of 20 minutes. Since articaine is hydrolyzed very quickly in the blood, the risk of systemic intoxication seems to be lower than with other anesthetics, especially if repeated injection is necessary. Other chemical and physical characteristics of articaine, such as protein binding, pKa, lipid solubility, lack of EDTA, and reduced amounts of potentially allergic sulfites/bisulfites, may also give it a decisive advantage over lidocaine.

References

8. Malamed, SF. Local anesthetics: Dentist most important drugs, Clinical Update, CDA Journal 2006; 34: 971-976. 9
10. Karayl V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta-analy-
13. Haze, DA, Lenon D. A 21-year retrospective study of reports of paralysis following local admin-
15. Ditas M. Is it safe to use articaine? Team Work 2010; 2(2); 28-35.
1) Which of the following is not a consideration in patients when determining the dose of articaine or lidocaine?
   A) Age
   B) Liver function
   C) Gender
   D) Body mass

2) Articaine was first introduced in what country?
   A) Italy
   B) United Kingdom
   C) Germany
   D) Canada

3) Articaine is metabolized primarily in the:
   A) Liver
   B) Kidney
   C) Plasma
   D) Intestine

4) Lidocaine is metabolized primarily in the liver and produces a metabolite named xylidide, which is in itself an anesthetic.
   A) True
   B) False

5) Some studies have demonstrated likely superiority of articaine versus lidocaine in what procedures or conditions?
   A) Irreversible pulpitis
   B) Mandibular block
   C) Bilateral extraction of maxillary premolars
   D) All of the above

6) The incidence of paresthesia when using articaine and lidocaine is:
   A) Less than 1 percent with either in controlled trials
   B) More frequent with articaine
   C) More frequent with lidocaine

7) The salinity (or isotonicity) of articaine and lidocaine help with which of the following:
   A) Absorption
   B) Elimination
   C) Pain upon injection
   D) Efficacy

8) When comparing products which characteristic of articaine is the most prominent advantage of use?
   A) Metabolism
   B) Lipid solubility
   C) pH
   D) Isotonicity

9) Epinephrine is preserved in both products using either the sodium or potassium salt of the antioxidant. The sodium salt is the preferred antioxidant.
   A) True
   B) False

10) Most lidocaine products use terminal sterilization (heat applied at the finish). Another method of sterilization is aseptic manufacturing where no heat is applied to the finished product. This process can result in an increased shelf life of:
    A) 3 months
    B) 6 months
    C) 12 months
    D) 16 months
Superiority of Articaine versus Lidocaine

by Fabio Velotti, Bernardo Verrengia & Deborah S. Laird

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Please evaluate this program by circling the corresponding numbers: (5 = Strongly Agree to 1 = Strongly Disagree)

1. Course administration was efficient and friendly
   5  4  3  2  1
2. Course objectives were consistent with the course as advertised
   5  4  3  2  1
3. COURSE OBJECTIVE #1 was adequately addressed and achieved
   5  4  3  2  1
4. COURSE OBJECTIVE #2 was adequately addressed and achieved
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5. COURSE OBJECTIVE #3 was adequately addressed and achieved
   5  4  3  2  1
6. COURSE OBJECTIVE #4 was adequately addressed and achieved
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13. Overall, I would rate this course (5 = Excellent to 1 = Poor):
    5  4  3  2  1
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    5  4  3  2  1
15. Overall, this course met my expectations
    5  4  3  2  1

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