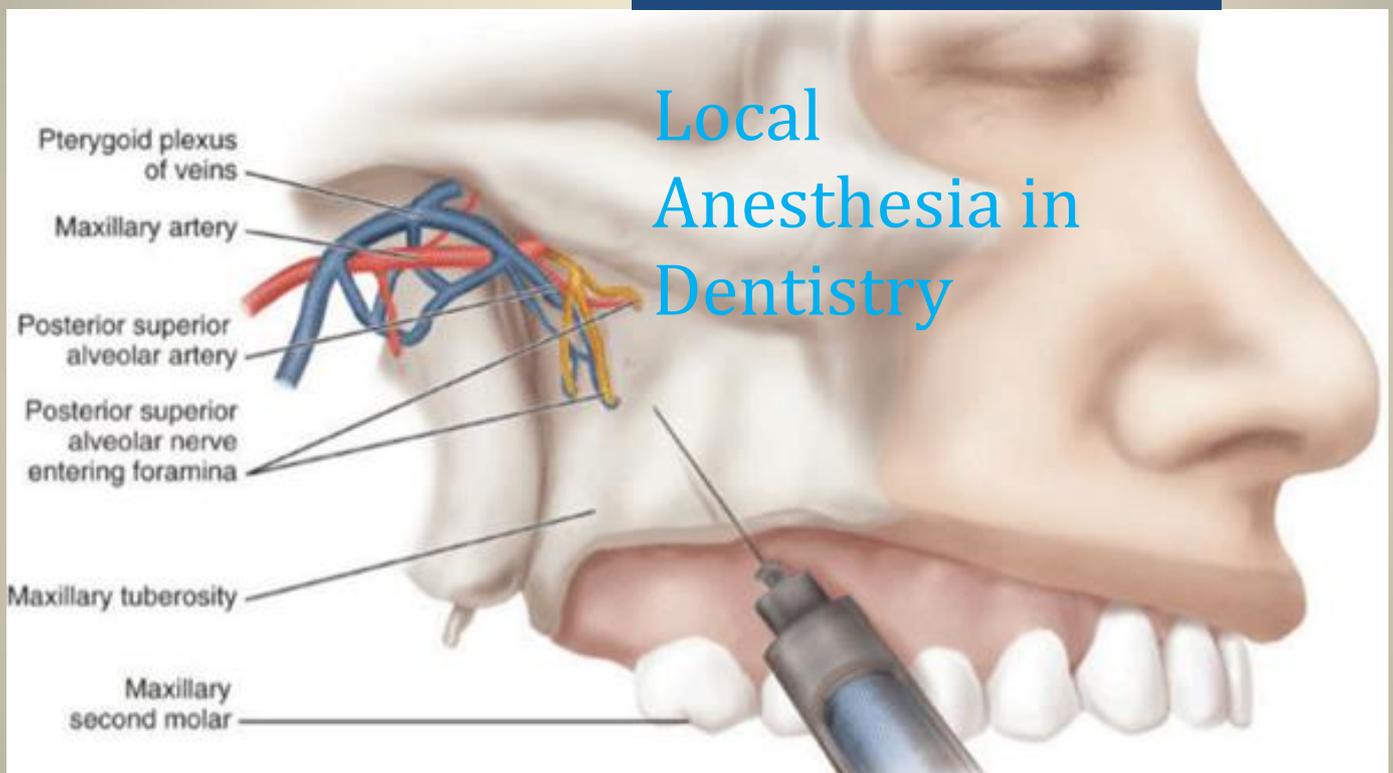


Sponsored by
Pierrel Pharma,
makers of Orabloc

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



Authors:

Fabio Velotti, M.Sc. Eng
Bernardo Verrengia, C. Chem MRSC
Deborah S. Laird, BS Pharm, RPh

Abstract

This paper is an illustration of articles and some scientific studies that have come into the dental anesthetics debate as of 2011 through 2015 including some historical information leading up to this point. It is mainly a discussion of the comparison of articaine 4% to lidocaine 2% regarding both drugs' safety and efficacy.

Yapp et al⁹ in an article in 2011 entitled "Articaine: Review of the literature" published in the British Dental Journal does 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 along side lidocaine in certain procedures such as intraosseous anesthesia in patients with irreversible pulpitis.¹⁰

Several more recent articles, Brandt et al¹¹ and Kaana et al¹², 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% at pH 8.3 and about 75% 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.¹³

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.

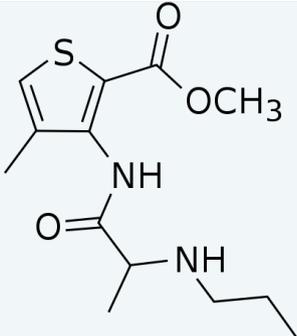
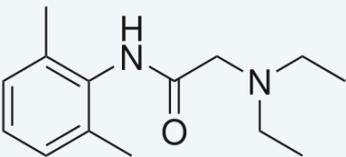
Parameter/substance	Articaine	Lidocaine
Chemical name	3-N-propylamino-propionyl-amino-2-carbomethoxy-4-methylthiophene hydrochloride	2-Diethylamino 2,6-acetoxylidide
Structural formula		
Classification	Amide	Amide
Molecular weight	284.38	234.34
pKa	7.8	7.9
Partition coefficient	2.07	2.44
Lipid solubility	1.5	4.0
Plasma protein binding	76%(pH 8.5) 54%(pH 7.5)	74%(pH 8.5) 61%(pH 7.5)

Table 1: Basic physical/chemical properties of articaine and lidocaine

Articaine has a lower pKa than lidocaine.

The metabolism of the two drugs is also different. As for the metabolism of articaine, a small amount (10%) is handled by the liver, but about 90% is hydrolyzed in the serum by non-specific blood esterases.¹⁴ In contrast, lidocaine is predominantly metabolized in the liver (70%) 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 performed¹⁵.

Efficacy

Yapp et al¹ in an article in 2011 entitled "Articaine: Review of the literature" published in the British Dental Journal does a more than adequate job of looking at articaine as a new injectable anesthetic (LA) entering the market. 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 along side lidocaine in certain procedures such as intraosseous anesthesia in patients with irreversible pulpitis.²

Several more recent articles, Brandt et al³ and Kaana et al⁴ discuss trials that also confirm the efficacy of articaine versus lidocaine in irreversible pulpitis.

A recent meta-analysis published by Kung, McDonagh and Sedgley¹⁶ in August 2015, showed superiority of articaine over lidocaine in patients with symptomatic irreversible pulpitis. 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 over the years have established the efficacy of articaine in local anesthesia (LA). Most of these studies were conducted using lidocaine as the comparator drug. More recent studies have shown some advantages of articaine versus lidocaine. Hassan et al¹⁶ 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. In addition, the use of articaine was said to eliminate the need for palatal injection that can be extremely painful.

Several meta-analyses have been conducted, Katyal¹⁷ et al and Brandt et al with the latter more recently. 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.

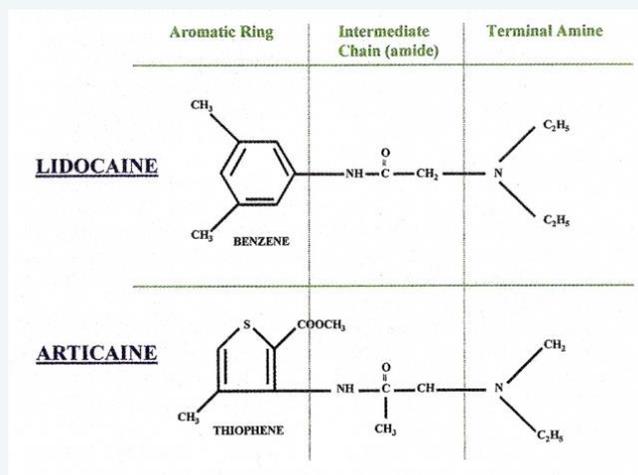
The sodium chloride content is much lower in articaine than in lidocaine. Sodium chloride is used to make the solutions for injection isotonic which helps to minimize the pain on injection. Articaine requires 1mg/mL of sodium chloride while lidocaine uses 6.5mg/mL for isotonicity.¹⁸ The osmolarities of the two products are very similar about 270-290 mOsm (micro-osmoles).

This brings them into the range of a 0.9% 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 of the drug product. 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) whilst some lidocaines use the potassium salt (potassium metabisulphite about 1.2 mg/ml)¹⁰. 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% were permitted. Today the maximum permitted overage of epinephrine is 15% (see USP Compendia formulations).

Sodium edetate (EDTA) was commonly used in LAs formulated in the 70's and 80's when high quality polished stainless steel (e.g., SS 316L) was not available for drug preparation tanks and solution transfer piping. Trace metals were often found in the products and subsequently EDTA was added to complex the metal ions to avoid coloration and/or precipitation in the final solutions. Articaine does not contain EDTA because there are more recent formulations and there have been technological advances in manufacturing equipment. Many lidocaine products still use EDTA (0.25 mg/ml)¹⁰. If EDTA is present there is some potential for allergic reactions related to the EDTA but the incidence is low. More important is the fact that today 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 controversy¹¹. This paper analyzed 143 cases reported to the Royal College of Dental Surgeons of Ontario (RCDSO) over a 21-year period. The results from their analysis seemed to indicate that 4% anesthetics had a higher incidence of causing paresthesia. The authors concluded that "...the overall incidence of paresthesia following local anesthesia administration for non-surgical 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 and 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% drugs has never been scientifically proven.¹⁹

Only a single controlled clinical study by Malamed et al has compared articaine to lidocaine in regard to safety and efficacy particularly paresthesia.²⁰ 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% with epinephrine 1:100,000 with lidocaine 2% 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% for articaine and 20% for the lidocaine group. The most frequently reported adverse events in the articaine group, excluding post procedural dental pain were headache (4%), facial edema, infection gingivitis

and paresthesia (1% each). 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 Haas²¹ 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.” There is significant literature documentation that 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 et al¹¹ 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 et al in 2008²², suggests that a quarter of dentists surveyed (n=373) used articaine regularly in children aged 2-3 years of age 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 et al¹, 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 are generally manufactured via an aseptic process. For example, drug products containing epinephrine, polypeptides and biotech drug products.

Commercial LAs containing epinephrine are manufactured by both methods since there is considerable heat sensitivity of epinephrine and metabisulphite. Today, in the US, only one articaine product uses aseptic manufacturing (Orabloc®, articaine 4% w/epinephrine, marketed by Pierrel Pharma) and in Europe, Ultracaine from Sanofi Aventis whilst all other LAs, 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 Considerations of Articaine Vs. Lidocaine

Lidocaine has been a standard of dental anesthesia for over 60 years. First synthesized under the name xylocaine (Astra AB), it has remained a staple of dental LA’s. Articaine was introduced as articaine in Germany in 1976 (Hoechst), the United Kingdom in 1998, the United States in 2000 and in Australia in 2005¹. Articaine formulation containing epinephrine 1:200,000 was only introduced in the US 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. Uptake in North America has been

slower since many dentists were trained in University using lidocaine as their primary LA and articaine was made available only in 2000 and 2005 whereas lidocaine was available in the US since the late 70's. 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% may suggest that half as much anesthetic need be used in patients in comparison with lidocaine 2% which sometimes may require multiple re-injections to establish adequate anesthesia.

Summary

Articaine is an amide anesthetic that is 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/physical characteristics of articaine such as protein binding, pKa, lipid solubility, lack of EDTA, and reduced amounts of potentially allergenic sulfites/bisulfites may also give a decisive advantage over lidocaine.

References

- ¹ Yapp KE, Hopcraft MS, Parashos P. Articaine: a review of the literature, *Br Dent J.* 2011; 210(7): 323-9.
- ² Bigby J, Reader A, Nusstein J, Beck M, Weaver J. Articaine for supplemental intraosseous anesthesia in patients with irreversible pulpitis. *J ENDO.* 2006; 32: 1044-1047.
- ³ Brandi R, Anderson P, McDonald N, Sohn W, Peters M. The pulpal anesthetic efficacy of articaine versus lidocaine in dentistry: A meta-analysis. *JADA* 2011; 142(5).
- ⁴ Kanaa MD, Whitworth JM, Meechan JG, A comparison of 4% articaine w/1:100,000 epinephrine and lidocaine w?1:80,000 epinephrine in achieving pulpal anesthesia in maxillary teeth with irreversible pulpitis. Elsevier Inc in PMID: 22341059. [PubMed 0 indexed for MEDLINE].

⁵ Ali SG, Mulya S. Articaine vs. lidocaine: A review. *IOSR Journal of Dental and Medical Sciences* 2014; 33: 417-425.

⁶ Oertel R, Rahn R, Kirch W. Clinical pharmacokinetics of articaine. *Clin Pharmacokinet* 1997; 33: 417-425.

⁷ Malamed, SF. Local anesthetics: Dentists most important drugs, *Clinical Update, CDA Journal* 2006; 34: 971-976. ⁸ Hassan S, Rao B, Sequeria J, Rai, G. Efficacy of 4% articaine HCl and 2% lignocaine HCl in the extraction of maxillary premolars for orthodontic reasons. *Annual J of Maxillofacial Surg,* Jan – Jun 2011. (1) (1).

⁹ Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta analysis. *J Dent.* 2010; 38(4); 307-17.

¹⁰ Prescribing Information; articaine hydrochloride and lidocaine hydrochloride, 2015.

¹¹ Haas, DA, Lennon D. 1 21-year retrospective study of reports of paresthesia following local administration. *J CAN DENT ASSOC,* 1195; 61(4); 319-20. 523-6, 329-30.

¹² Diaz M. Is it safe to use articaine? *Team Work* 2010, 2(2); 28-35,

¹³ Malamed SF, Gagnon S, LeBlanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. *J Am Dent Assoc* 2001, 132(2); 177-85.

¹⁴ Gaffen AS, Haas DA. Retrospective review of voluntary reports of non-surgical paresthesia in dentistry. *J CAN Dent Assoc.* 2009; 75(8); 579-579f.

¹⁴ Brickhouse TH, Webb M, Best AM, Hollowell RL. Articaine in children among dental practitioners. *Pediatr Dent* 2008; 30: 516-521.

¹⁵ Kung J, McDonagh M, Sedgley C. Does Articaine Provide an Advantage over Lidocaine in Patients with Symptomatic Irreversible Pulpitis? A Systematic Review and Meta-Analysis. *J Endo.* Nov 2015, Vol 41, Issue 11, 1784-1794.

