



A comparison between Articaine HCl and Lidocaine HCl in pediatric dental patients

Stanley F. Malamed, DDS Suzanne Gagnon, MD Dominique Leblanc, D Pharm

Dr. Malamed is professor of Anesthesia & Medicine at the School of Dentistry for the University of Southern California; Dr. Gagnon is vice president of Medical Affairs for IBAH Inc.; Dominique Leblanc is Scientific Director for Specialties Septodont. Correspond with Dr. Malamed at malamed@hsc.usc.edu

Abstract

Purpose: Three identical single-dose, randomized, double-blind, parallel-group, active-controlled multicenter studies were conducted to compare the safety and efficacy of articaine HCl (4% with epinephrine 1:100,000) to that of lidocaine HCl (2% with epinephrine 1:100,000) in patients aged 4 years to 79 years, with subgroup analysis on subjects 4 to <13 years.

Methods: Fifty subjects under the age of 13 years were treated in the articaine group and 20 subjects under the age of 13 were treated with lidocaine. Subjects were randomized in a 2:1 ratio to receive articaine or lidocaine. Efficacy was determined on a gross scale immediately following the procedure by having both the subject and investigator rate the pain experienced by the subject during the procedure using a visual analog scale (VAS). Safety was evaluated by measuring vital signs before and after administration of anesthetic (1 and 5 minutes post-medication and at the end of the procedure) and by assessing adverse events throughout the study. Adverse events were elicited during telephone follow-up at 24 hours and 7 days after the procedure.

Results: Pediatric patients received equal volumes, but higher mg/kg doses, of articaine than lidocaine during both simple and complex dental procedures. Pain ratings: Articaine: VAS (Visual Analogue Scale) scores (from 0 to 10 cm) by patients 4 to <13 years of age were 0.5 for simple procedures and 1.1 for complex procedures, and average investigator scores were 0.4 and 0.6 for simple and complex procedures, respectively. Lidocaine: patients 0.7 (simple) and 2.3 (complex); investigators 0.3 (simple) and 2.8 (complex). Adverse events: No serious adverse events related to the articaine occurred. The only adverse event considered related to articaine was accidental lip injury in one patient.

Conclusions: VAS scores indicate that articaine is an effective local anesthetic in children and that articaine is as effective as lidocaine when measured on this gross scale. Articaine 4% with epinephrine 1:100,000 is a safe and effective local anesthetic for use in pediatric dentistry. Time to onset and duration of anesthesia are appropriate for clinical use and are comparable to those observed for other commercially available local anesthetics. (*Pediatr Dent* 22:307-311, 2000)

Since the introduction of cocaine local anesthesia in 1886, and the subsequent development of procaine (1904) and other related ester-type anesthetics, dentistry has prided itself on being as close to "painless" as possible. Nowhere is this concept more important than in the management of children. In the late 1940s a new group of local anesthetic compounds,

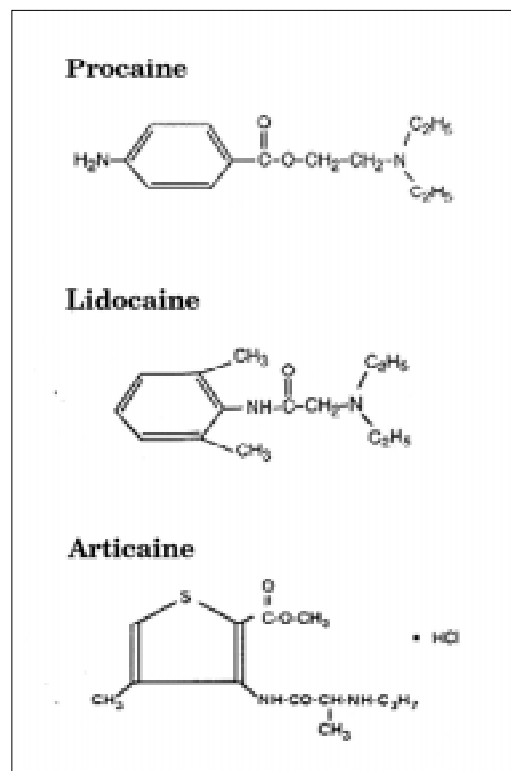


Fig 1. Chemical structure of procaine, lidocaine and articaine.

the amides, was introduced. The initial amide local anesthetic, lidocaine (Xylocaine[®]), revolutionized pain control in dentistry worldwide. In succeeding years, other amide local anesthetics (mepivacaine, prilocaine, bupivacaine, and etidocaine) were introduced. They gave the dental practitioner a local anesthetic armamentarium which provided pulpal anesthesia for periods of from 20 minutes (mepivacaine) to as long as three hours (bupivacaine and etidocaine with epinephrine). In addition, these popular drugs proved to be more rapid-acting than the older ester-type drugs and, at least from the perspective of allergenicity, safer.

In 1976, a new amide local anesthetic, articaine HCl was introduced. Articaine (the generic name was changed) possesses clinical actions similar to lidocaine but has additional properties which make the drug quite attractive in dentistry.

Table 1. Demographics: Patients 4 to <13 Years of Age

	<i>Articaine 4% with epinephrine 1:100,000</i>	<i>Lidocaine 2% with epinephrine 1:100,000</i>	<i>Total</i>
Total no. of treated subjects	50	20	70
<i>Sex N (%)</i>			
Female	21 (42%)	13 (65%)	34 (49%)
Male	29 (58%)	7 (35%)	36 (51%)
<i>Race N (%)</i>			
White	10 (20%)	5 (25%)	15 (21%)
Black	6 (12%)	0 (0%)	6 (9%)
Asian	2 (4%)	1 (5%)	3 (4%)
Hispanic	32 (64%)	14 (70%)	46 (66%)

Articaine (articaine) hydrochloride was prepared by Rusching et al. in 1969 and has a molecular weight of 320.84.¹ Articaine is unique among local anesthetics in that it is the only local anesthetic which possesses a thiophene group [in place of a benzene ring] (Fig 1). Additionally, articaine is the only widely used local anesthetic that also contains an ester group. Because of this the biotransformation of articaine occurs in both the plasma (hydrolysis by plasma esterase) and liver (hepatic microsomal enzymes). Articainic acid, the primary metabolite, is pharmacologically inactive. Articaine is eliminated via the kidneys. Approximately 5% to 10% is excreted unchanged.²

Possessing many of the physicochemical properties of other local anesthetics, with the exception of the thiophene moiety and its degree of protein binding, articaine penetrates well into tissue and is highly diffusible. Its plasma protein binding of approximately 95% is higher than that observed with many local anesthetics. The thiophene ring of articaine increases its liposolubility (and potency).

The mechanism by which articaine blocks nerve conduction is similar to that of lidocaine, mepivacaine and prilocaine.³ Addition of a vasopressor produces localized vasoconstriction which retards the absorption of articaine, leading to a prolonged maintenance of an active tissue concentration of articaine as well as minimizing the systemic absorption of both active compounds (articaine/epinephrine).

Clinical trials comparing the time to onset of clinical anesthesia and the duration and depth of anesthesia with 1%, 2%, 3%, and 4% articaine, with and without a vasopressor, to at least one other local anesthetic have shown that 4% articaine (with epinephrine) provides a significantly shorter time to onset of anesthesia as well as a greater consistency in both the onset and duration of anesthesia than 2% articaine with the same epinephrine concentration.⁴⁻⁹ Lower concentrations of articaine were less effective than 4% articaine in time of onset, duration, and effectiveness of anesthesia. Importantly, no differences in toxicity were noted between 4% articaine and lower concentrations. Published data indicate that for consistent efficacy, including onset and duration of anesthesia, 4% articaine is preferable to a lower concentration.⁴⁻⁹

In pharmacokinetic/pharmacodynamic studies, the duration of soft tissue anesthesia produced by 4% articaine with a dose of 1.8 ml. was reported as 2.6 to 4.5 hours for maxillary infiltration and 4.3 to 5.3 hours for nerve block.^{10,11} The mean duration of pulpal anesthesia (as determined by electric pulp testing) was 68+/-8 minutes (range: 20-175m) using 4%

articaine with epinephrine 1:200,000. Complete anesthesia was achieved in all subjects (N=20).¹²

The anesthetic activity of articaine/epinephrine combinations has been demonstrated to be comparable to that of other anesthetic combinations, including lidocaine/epinephrine; mepivacaine/levonordefrin; and prilocaine/epinephrine.

Several studies reported the successful use of articaine with epinephrine in children. Dudkiewicz et al. (1987) reported successful anesthesia in all cases for 50 children (84 treatments) 4 to 10 years of age.¹³ These children received up to 2.7 mL of articaine 4% with epinephrine 1:100,000 or 200,000, as mandibular infiltration for restorative treatment of primary molars and canines. Wright et al. (1991) examined the effectiveness of three different anesthetics administered as mandibular infiltration to 66 children, 42-78 months old (3.5 to 6.5 years).¹⁴ Twenty-five of the 66 children received articaine 4% with epinephrine 1:200,000. All children were rated as to comfort, pain, and cooperative behavior according to two observational scales completed by a single independent rater who viewed videotapes of the procedures. All three anesthetics were equally effective, with no statistically significant differences between articaine and the other two anesthetics.

Lemay et al. (1985)¹⁰ and Donaldson et al. (1987)¹⁵ found that the mean time to onset of anesthesia with articaine was generally shorter for children than for adults. Following nerve block with articaine 4% with epinephrine 1:200,000, time to onset of anesthesia was 168±131 sec for children versus 170±131 sec for adults. For infiltration it was 85±60 sec (children) and 119±84 sec (adults).¹⁰ Donaldson found similar results: time to onset of anesthesia following nerve block was 58±27 sec for children versus 113±52 sec for adults; for infiltration onset was 60±46 sec for children versus 106±45 sec for adults.¹⁵

Articaine's excellent pediatric safety and efficacy profile is supported by other studies in the literature. A retrospective study on the use of articaine local anesthesia in children under 4 years of age was compiled by Wright et al. (1989)¹⁶ Data were collected from two pediatric dental offices in Canada and included the charts of 211 pediatric patients, 29 of whom received additional administrations. In all cases patients received articaine 4% with epinephrine either 1:100,000 or 1:200,000. Data were collected into two groups: children who received sedation in addition to local anesthesia, and all children who received local anesthesia. Weights were available for children who received sedation making it possible to calculate the mg/kg dosage of local anesthetic administered. Eighteen of 64 se-

Table 2. Study Drug Administration: Comparison of Articaine 4% With Epinephrine 1:100,000 to Lidocaine 2% With Epinephrine 1:100,000

	<i>Articaine 4% with epinephrine 1:100,000</i>		<i>Lidocaine 2% with epinephrine 1:100,000</i>	
	Simple	Complex	Simple	Complex
Number of subjects	43	7	18	2
Mean volume ± SEM (mL)	1.9 ± 0.10	2.5 ± 0.43	1.9 ± 0.23	2.6 ± 0.00
Mean dose ± SEM (mg/kg)	2.37 ± 0.182	2.91 ± 1.009	1.27 ± 0.144	1.43 ± 0.296

dated patients received dosages in excess of 7 mg/kg, and one child received more than 11 mg/kg, all without adverse effects. In total, 211 patients received a total of 240 doses of articaine without adverse effects reported in the medical records.

An open study of the anesthetic potential of articaine in 50 children between the ages of 4–10 years was performed by Dudkiewicz et al. (1987).¹³ Twenty-six boys and 24 girls received articaine 4% with epinephrine 1:100,000 or 1:200,000 in mandibular infiltration, mandibular blocks, and oral surgery. Doses given ranged from 0.3 to 2.5 mL, 0.3 to 3.4 mL, and 1.0 to 5.1 mL, respectively. Doses did not exceed 5 mg/kg body weight in children between the ages of 4 and 10 years. Eighty-four treatments were provided by two clinicians. Anesthesia was successful in all cases, although there were a few instances where a child complained of pain at the beginning of the procedure, necessitating an additional 5 minute waiting period. No adverse effects were reported.

This paper reports the results of a clinical program consisting of three studies designed to compare the efficacy and the safety of articaine HCl (“articaine”) 4% with epinephrine 1:100,000 to that of lidocaine HCl (“lidocaine”) 2% with epinephrine 1:100,000 in patients aged 4 to 79 years, with subgroup analysis on subjects 4 years to <13 years.

Methods and materials

Three identical single-dose, randomized, double-blinded, parallel-group, active-controlled, multicenter studies were conducted to compare the safety and efficacy of articaine (4% with epinephrine 1:100,000) to that of lidocaine (2% with epinephrine 1:100,000) in subjects aged 4 to 79 years. Subjects 4 to <13 years of age were treated at a total of 7 sites in the United Kingdom and United States.

These pediatric subjects undergoing general dental procedures were stratified according to the procedure being performed into simple and complex groups.

All subjects were randomized in a 2:1 ratio to receive articaine or lidocaine, with the pediatric population ultimately receiving the anesthetics in a 2.5:1 ratio. A 2:1 articaine to lidocaine ratio was employed to enable the gathering of more information regarding the efficacy and safety of this relatively new amide-type local anesthetic. The lowest effective dose of anesthesia was administered as submucosal infiltration and/or nerve block. Total dose was not to exceed 7.0 mg/kg of body weight.

Efficacy was determined on a gross scale immediately following the procedure by having both the subject and investigator rate the pain experienced by the subject during the procedure using a visual analog scale (VAS). The 10 cm VAS scale ranged from “it didn’t hurt” (smiley face = 0) to “worst hurt imaginable” (frowning face = 10) (Fig 2). The method of marking the scale was explained to the child by a parent or guardian, so that the investigator could be assured that the child thoroughly understood what he/she was being asked to do. The investigator marked a 10 cm scale identical to the one given to the patient to indicate his/her opinion of the patient’s pain during the procedure.

Safety was evaluated by measuring vital signs before and after administration of anesthetic (1 and 5 minutes post-medication and at the end of the procedure) and by assessing adverse events throughout the study. Adverse events were elicited during telephone follow-up at 24 hours and 7 days after the procedure.

The numbers of subjects between the ages of 4 and <13 years enrolled and treated in the three trials are summarized in Table 1. All studies followed accepted clinical practice procedures.

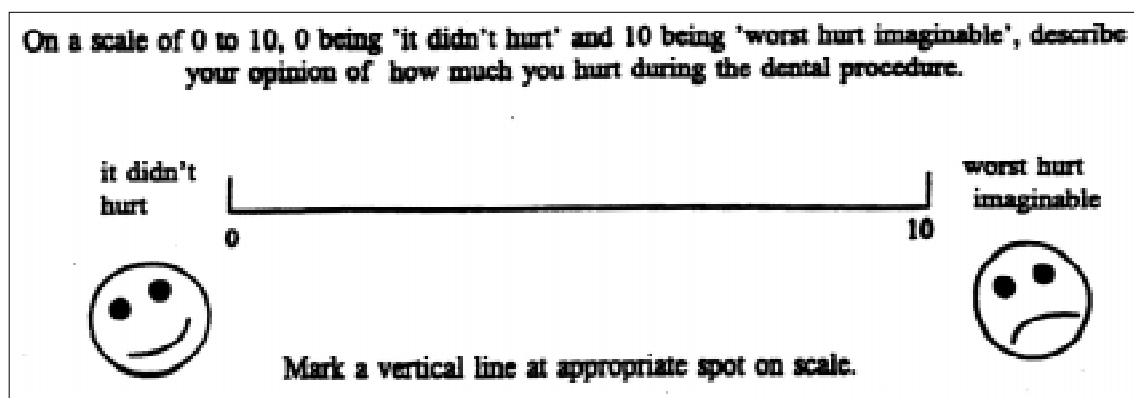


Fig 2. Pediatric and adult VAS criteria.

Results

Subject demographics: Fifty subjects under the age of 13 years were treated with articaine and 20 subjects under the age of 13 were treated with lidocaine. Table 1 summarizes patient demographics for each group.

Efficacy

Drug volumes: Study drug administration for all enrolled patients (N = 70) is summarized in Table 2. Patients received comparable volumes of articaine and lidocaine for both simple and complex procedures, but higher mg/kg doses of articaine in both types of procedures due to the higher concentration of articaine (4%) versus lidocaine (2%). Mg/kg articaine: 2.37±0.182 (simple), 2.91 ± 1.009 (complex); lidocaine: 1.27 ± 0.144 (simple), 1.43 ± 0.296 (complex). One patient received articaine in excess of the maximum recommended dose of 7.0 mg/kg (5 yo/18 kg). No adverse event or other sequelae developed in this patient.

Duration of procedures: The average duration of simple and complex procedures was comparable between the articaine and lidocaine groups. Duration of simple procedures was 16±2.46 minutes in the articaine group and 19±5 minutes in the lidocaine group. For complex procedures the averages were 69±19.99 and 57±55.55 minutes, respectively. The range of procedures was wide, such that the longest procedures took over 2.3 hours to complete.

Pain ratings: VAS scores for patients 4 to <13 years of age are found in Table 3. For the articaine group, the mean patient scores were 0.5±0.18 for simple procedures and 1.1±0.33 for complex procedures, while the average investigator scores ranged from 0.4±0.14 to 0.6±0.28. These scores indicate that articaine is an effective local anesthetic when used in children. Mean patient VAS scores for the lidocaine group were 0.7±0.26 (simple) and 2.3±2.25 (complex).

Safety

Adverse events: No serious adverse events related to the study medication occurred. At least one minor adverse event was reported by 8% (4/50) of articaine patients, and 10% (2/20) of lidocaine patients reported at least one minor adverse event. Adverse events noted in the articaine group were post-procedural pain (2%), headache (2%), injection site pain (2%), and accidental injury (2%). In the lidocaine group the most common minor adverse event was post-procedural pain (10%). Table 4 summarizes all adverse events reported.

The one patient who received more than the recommended maximum dosage of 7.0 mg/kg of articaine reported no adverse events.

Among patients 4 to <13 years of age, the only adverse event directly related to articaine was accidental lip injury.

Vital signs: For patients 4 to <13 years old, mean supine blood pressure values increased slightly from baseline after administration of the study drug, as opposed to slight decreases seen in the population as a whole. These changes were not clinically significant and were not associated with any adverse events.

Discussion

Efficacy: Efficacy of articaine was evaluated among 50 children between 4 and <13 years of age. Mean pain (VAS) scores were slightly higher among the children when compared with the adult age groups. Overall pain was judged greatest by the children undergoing complex procedures, but these scores were still very low (mean VAS: 1.1±0.33; range 0–2.5; median 0.7).

Safety: Adverse events were reported by 4/50 (8%) of the children in the articaine group and 2/20 (10%) of the children in the lidocaine group. Table 4 lists all adverse events in this age group.

Of the four adverse events reported in children in the articaine group, only accidental injury (a lip bite) was considered to be related to the study drug. It was mild in severity. There were no serious adverse events, no discontinuations due to adverse events, or deaths in children. The overall occurrence of adverse events in children was somewhat less than in the population as a whole (8% of patients 4 to <13 years of age, as compared to 22% of all patients in the articaine group).

Articaine was well tolerated by 50 subjects between 4 and <13 years of age who received the drug in these clinical trials. Although no allergic reactions were seen in these trials, articaine with epinephrine is contraindicated in patients with known sensitivity to amide-type local anesthetics and patients with sulfite sensitivity (such as some asthmatics with allergic-type asthma). Articaine should be used with caution in patients with hepatic disease and significant impairments in cardiovascular function since amide-type local anesthetics undergo biotransformation in the liver and possess myocardial depressant properties. Safe use in pregnancy and lactation has not been established. Use in children under 4 years of age is not recommended, since no data exist to support such usage.

Articaine 4% with epinephrine 1:100,000 is safe and effective when administered by injection to children at least 4 years of age.

Table 3. Summary of VAS Pain Scores (0–10 cm) Stratified by Complexity of Procedure

Procedure	4% articaine + epinephrine 1:100,000		2% lidocaine + epinephrine 1:100,000		p-value*
	Simple	Complex	Simple	Complex	
Number of subjects	43	7	18	2	
Investigator score (cm)					
Mean	0.4	0.6	0.3	2.8	0.569
Range	0–4.1	0–2.1	0–1.2	2.2–3.4	
Patient score (cm)					
Mean	0.5	1.1	0.7	2.3	0.416
Range	0–5.5	0–2.5	0–3.0	0–4.5	

* Two-sided p-value from a Kruskal-Wallis test comparing treatment groups

Table 4. Adverse Events Reported by Patients 4 to <13 Years Old

<i>Body system/Adverse event</i>	<i>Articaine 4% with epinephrine 1:100,000 (N = 50)</i>	<i>Lidocaine 2% with epinephrine 1:100,000 (N = 20)</i>
Patients with at least one event	4 (8%)	2 (10%)
Body as a whole		
Accidental injury	1 (2%)	0
Headache	1 (2%)	0
Injection site pain	1 (2%)	0
Pain	1 (2%)	2 (10%)

Conclusion

Articaine 4% with epinephrine 1:100,000 is a safe and effective local anesthetic for use in pediatric dentistry. Time to onset and duration of anesthesia are appropriate for clinical use and are comparable to those observed for other commercially available local anesthetics. Articaine can be used effectively in children.

Articaine 4% with epinephrine 1:100,000 provides total pain relief during most dental procedures. In these randomized, double-blind studies, no significant difference in pain relief was observed between articaine 4% with epinephrine 1:100,000 and lidocaine 2% with epinephrine 1:100,000.

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Primary investigators in pediatric portion of this study:

- Louie Al-Farage, MD, DDS, San Diego, CA
- Ian M. Brook, BDS, MDS, PhD, FDSRCS, Sheffield, Great Britain
- Alan R. Brown, DDS, FACD, Kansas City, MO
- Martin E. J. Curzon, BDS, LDSRCS, MSc, PhD, FRCD(c), FDSRCS, Leeds, Great Britain
- Claire J. Gill, PharmD, DDS, Los Angeles CA
- Theodore A. Kiersch, DDS, Tuscon, AZ
- Stanley F. Malamed, DDS, Los Angeles CA
- Raymond A. Yukna, DMD, MS, New Orleans LA