

# EFFICACY OF ARTICAININE: A NEW AMIDE LOCAL ANESTHETIC

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## ABSTRACT

**Background.** The authors compared the safety and efficacy of 4 percent articaine with epinephrine 1:100,000 with 2 percent lidocaine with epinephrine 1:100,000.

**Methods.** In three identical randomized, double-blind, multicenter trials, subjects 4 to 80 years of age received either 4 percent articaine with epinephrine 1:100,000 or 2 percent lidocaine with epinephrine 1:100,000 for simple or complex dental procedures. In each trial, the authors randomized the subjects in a 2:1 ratio to receive articaine or lidocaine. Efficacy was determined by both subject and investigator using a visual analog scale, or VAS. The authors used the Kruskal-Wallis test to analyze the data.

**Results.** A total of 882 subjects received articaine, and 443 received lidocaine. The authors found no statistical differences between the groups ( $P = .05$ ). They also compared drug volumes for both articaine and lidocaine groups (2.5 milliliters  $\pm$  0.07 standard error of mean, or SEM, vs. 2.6 mL  $\pm$  0.09 SEM for simple procedures and 4.2 mL  $\pm$  0.15 SEM vs. 4.5 mL  $\pm$  0.21 SEM for complex procedures). The

procedures' durations were comparable for both the articaine and lidocaine groups. The authors found no statistical difference between the two treatment groups ( $P = .05$ ) with respect to subject or investigator pain ratings using the VAS; the mean pain scores determined by both patients and investigators for all groups tested were less than 1.0.

**Conclusions.** The authors found that 4 percent articaine with epinephrine 1:100,000 was well-tolerated in 882 subjects. It also provided clinically effective pain relief during most dental procedures and had a time to onset and duration of anesthesia appropriate for clinical use and comparable to those observed for other commercially available local anesthetics.

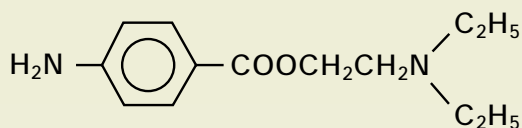
**Clinical Implications.** Pain control is a major component of patient comfort and safety. Local anesthetics form the backbone of pain control techniques in dentistry. Four percent articaine with epinephrine is an amide local anesthetic that will meet the clinical requirements for pain control of most dental procedures in most patients.

**C**articaine, first prepared by Rusching and colleagues in 1969, had its generic name changed to articaine when it entered clinical practice in Germany in 1976.<sup>1</sup> Its use gradually spread, entering North America in Canada in 1983,<sup>2</sup> and the United Kingdom in 1998.

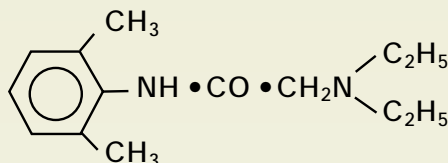
Articaine is 4-methyl-3-(2-[propylamino]propionamido)-2-thiophenecarboxylic acid, methyl ester hydrochloride with a molecular weight of 320.84 (Figure). It is the only amide local anesthetic that contains a thiophene ring. In addition,

articaine is the only widely used amide local anesthetic that contains an additional ester ring. Biotransformation of articaine occurs in both the plasma (hydrolysis by plasma esterase) and the liver (hepatic microsomal enzymes). Degradation of articaine is initiated by hydrolysis of the carboxylic acid ester groups to give free carboxylic acid.<sup>3</sup> Articaic acid is the primary metabolite, or M<sub>1</sub>.<sup>3</sup> Additional inactive metabolites, or M<sub>2</sub>, have been detected in animal studies.<sup>4</sup> Articaine is eliminated via the kidneys. Approximately 5 to 10

**PROCAINE**



**LIDOCAINE**



**ARTICAINE**

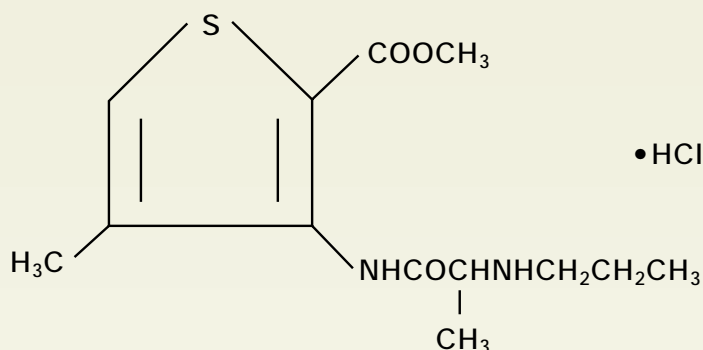


Figure. Chemical structures of procaine, lidocaine and articaine.

percent is excreted unchanged, and 89 percent is excreted as metabolites: M<sub>1</sub> at 87 percent and M<sub>2</sub> at 2 percent.<sup>5</sup>

Articaine has many of the physicochemical properties of the most commonly used local anesthetics (lidocaine, mepivacaine and prilocaine) with the exception of the aromatic ring and its degree of protein binding (Table 1). Articaine effectively penetrates tissue and is highly diffusible. Its plasma protein binding of approximately 95 percent is higher than that observed with many local anesthetics. Additionally, the thiophene ring of articaine increases its liposolubility.

Articaine reversibly inhibits conduction of nerve impulses by blocking sodium and potassium channels during propagation of the nerve action potential through an action mechanism similar to that of other amide local anesthetics—such as lidocaine, prilocaine and bupivacaine—used in dental practice. Including epinephrine produces localized vasoconstriction, which slows the absorption of

TABLE 1

PHARMACOKINETIC PROPERTIES OF COMMON DENTAL LOCAL ANESTHETICS.

LOCAL ANESTHETIC	pKa* (pH)	ONSET	LIPID SOLUBILITY†	USUAL PERCENTAGE OF DRUG USED IN ANESTHETIC	PROTEIN BINDING (%)	DURATION
<b>Articaine</b>	7.8	Fast	1.5	4	95	Moderate
<b>Bupivacaine</b>	8.1	Moderate	30.0	0.5 to 0.75	95	Long
<b>Etidocaine</b>	7.9	Fast	140.0	1.5	94	Long
<b>Lidocaine</b>	7.8	Fast	4.0	2	65	Moderate
<b>Mepivacaine</b>	7.7	Fast	1.0	2 to 3	75	Moderate
<b>Prilocaine</b>	7.9	Fast	1.5	4	55	Moderate
<b>Procaine</b>	9.1	Slow	1.0	2 to 4	5	Short

\* pKa is a dissociation constant.  
 † Lipid solubility is a ratio, using procaine as 1.

articaine. This ensures the prolonged maintenance of an active tissue concentration of the anesthetic, as well as minimizing the systemic absorption of both active compounds.

Articaine is used clinically in a 4 percent concentration. Published studies of both controlled and uncontrolled clinical trials have compared 1, 2, 3 and 4 percent articaine with and without epinephrine with at least one other anesthetic.<sup>6-11</sup> These studies demonstrate that the time of onset of anesthesia is significantly shorter with 4 percent articaine with epinephrine 1:200,000 compared with 2 percent articaine with epinephrine 1:200,000. There also appears to be a higher variability among patients in the onset and duration of anesthesia with the 2 percent solution. None of the lower concentrations were found to be superior to 4 percent articaine in time of onset, duration or effectiveness of anesthesia. No toxicity differences were reported between 2 percent and 4 percent articaine, either.

The onset of anesthesia with 4 percent articaine with epinephrine 1:200,000 is 1.5 to 1.8 minutes for maxillary infiltration and 1.4 to 3.6 minutes for inferior alveolar nerve block.<sup>2,12</sup> In an open study comparing articaine with epinephrine 1:100,000 to articaine with epinephrine 1:200,000, Lemay and colleagues,<sup>13</sup> found an average time to onset of anesthesia (as determined by electrical stimulation of the pulp) for both concentrations to be 120.8 seconds. With nerve block anesthesia, a more rapid onset was obtained with the 1:100,000 concentration than the 1:200,000 concentration (122.1 seconds  $\pm$  56.4 standard

## EXCLUSION CRITERIA.

- **Pregnancy**
- **Bony, fully impacted teeth or maxillofacial surgery**
- **Known or suspected allergies or sensitivities to sulfites, amide-type local anesthetics or any ingredients in the anesthetic solutions**
- **Concomitant cardiac or neurological disease**
- **History of severe shock, paroxysmal tachycardia, frequent dysrhythmia, severe untreated hypertension or bronchial asthma**
- **Evidence of soft-tissue infection near the proposed injection site (localized periapical or periodontal infections were permitted)**
- **Concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs**
- **Subjects requiring chloroform, halothane, cyclopropane, trichloroethylene or related anesthetics during the treatment visit**
- **Subjects who were expected to require nitrous oxide if anxious or any topical or general anesthesia (topical anesthesia was allowed in the United Kingdom study)**
- **Subjects who had taken aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs or other analgesic agents within 24 hours before administration of the study medication**

error of mean, or SEM, vs. 170.0 seconds  $\pm$  130.5 SEM, respectively); this difference, however, was not apparent with maxillary infiltration (105.0 seconds  $\pm$  49.2 SEM vs. 118.6 seconds  $\pm$  83.6 SEM, respectively).

In a clinical trial evaluating the anesthetic activity of 4 percent articaine with epinephrine 1:200,000 in 20 healthy volunteers (S.F.M., unpublished data, 1998) (the same formulation except for the epinephrine concentration used in the three multicenter trials discussed in the article), the mean duration of pulpal anesthesia (as determined by electric pulp testing) was 68.2 minutes  $\pm$  8.3 SEM (range, 20-175 minutes). Complete anesthesia was achieved in all subjects.

Other studies using 4 percent articaine with epinephrine combinations demonstrated similar results.<sup>8-13,14</sup> The duration of soft tissue anesthesia was 2.25 hours for maxillary infiltration and approximately 4.0 hours for nerve block.<sup>12</sup> Lemay and colleagues<sup>13</sup> reported anesthetic durations with a dose of 1.8 milliliters of 2.6 to 4.5 hours for maxillary infiltration and 4.3 to 5.3 hours for nerve block.

The anesthetic activity of articaine with epinephrine combinations has been demonstrated to be comparable to that of other anesthetic combinations, including lidocaine with epinephrine (U.S., U.K.), mepivacaine with epinephrine (U.K.) or with levonordefrin (U.S.), mepivacaine with norepineph-

TABLE 2

PATIENT DEMOGRAPHICS.			
DEMOGRAPHICS	4 PERCENT ARTICAINE WITH EPINEPHRINE 1:100,000	2 PERCENT LIDOCAINE WITH EPINEPHRINE 1:100,000	TOTAL
<b>Total No. of Treated Subjects</b>	882	443	1,325
<b>Age (Years) N (%)</b>			
4 to 12	50 (6)	20 (5)	70 (5)
13 to 64	778 (88)	396 (89)	1,174 (89)
65 to 74	43 (5)	23 (5)	66 (5)
75 and Older	11 (1)	4 (1)	15 (1)
Mean ± SEM*	36.2 ± 0.52	36.5 ± 0.73	36.3 ± 0.42
<b>Mean Weight in Kilograms ± SEM</b>	72.3 ± 0.62 (n = 879)	70.9 ± 0.86 (n = 438)	71.9 ± 0.51 (n = 1,317)
<b>Sex N (%)</b>			
Female	464 (53)	259 (58)	723 (55)
Male	418 (47)	184 (42)	602 (45)
<b>Race N (%)</b>			
White	647 (73)	330 (74)	977 (74)
Black	74 (8)	34 (8)	108 (8)
Asian	44 (5)	27 (6)	71 (5)
Hispanic	94 (11)	42 (9)	136 (10)
Other	23 (3)	10 (2)	33 (2)

\* SEM: Standard error of mean.

rine (U.K.), and prilocaine with epinephrine (U.S.).

In this article, we present the results of a clinical investigation consisting of three studies designed to compare the safety and efficacy of 4 percent articaine with epinephrine 1:100,000 with that of 2 percent lidocaine with epinephrine 1:100,000.

**METHODS**

We conducted three identical single-dose, randomized, double-blinded, parallel-group, active-controlled multicenter trials to compare the safety and efficacy of 4 percent articaine

with epinephrine 1:100,000 with that of 2 percent lidocaine with epinephrine 1:100,000. We conducted the trials at 27 sites (eight in the United Kingdom, 19 in the United States). The three trials were identical in all material respects.

At each site, subjects 4 to 80 years of age undergoing general dental procedures were stratified into one of two groups according to the complexity of the procedure being performed. The procedures performed in the “simple” group included single extractions with no complications, routine operative procedures, single apical resec-

tions and single crown procedures. The procedures performed in the “complex” group included multiple extractions; multiple crowns, bridge procedures or both; multiple apical resections; alveolectomies; mucogingival operations; and other osseous surgical procedures. We used the exclusion criteria listed in the box.

Within each stratum, we randomized subjects in a 2:1 ratio to receive articaine or lidocaine (both formulas contained epinephrine 1:100,000). We used the 2:1 articaine/lidocaine ratio so that fewer subjects could be enrolled (the safety

TABLE 3

SUBJECTS, VOLUME AND DOSE OF ARTICHAINE AND LIDOCAINE FORMULATIONS FOR SIMPLE AND COMPLEX PROCEDURES.				
PARAMETER	4 PERCENT ARTICHAINE WITH EPINEPHRINE 1:100,000		2 PERCENT LIDOCAINE WITH EPINEPHRINE 1:100,000	
	Simple	Complex	Simple	Complex
<b>Number of Subjects</b>	675	207	338	104*
<b>Mean Volume ± SEM† (Milliliters)</b>	2.5 ± 0.07	4.2 ± 0.15	2.6 ± 0.09	4.5 ± 0.21
<b>Mean Dose ± SEM (Milligrams per Kilogram)</b>	1.48 ± 0.042	2.36 ± 0.094	0.80 ± 0.031	1.26 ± 0.065
* Data are missing for one subject. † SEM: Standard error of mean.				

TABLE 4

DURATION OF SIMPLE AND COMPLEX PROCEDURES.				
PARAMETER	4 PERCENT ARTICHAINE WITH EPINEPHRINE 1:100,000		2 PERCENT LIDOCAINE WITH EPINEPHRINE 1:100,000	
	Simple	Complex	Simple	Complex
<b>Number of Subjects</b>	675*	207	338†	105*
<b>Mean Duration ± SEM‡ (Minutes)</b>	36.4 ± 1.28	58.3 ± 3.07	37.7 ± 2.01	52.6 ± 3.99
<b>Range (Minutes)</b>	0 to 217	1 to 215	0 to 220	1 to 171
* Data are missing for one patient. † Data are missing for two patients. ‡ SEM: Standard error of mean.				

and efficacy profile of lidocaine already is well-known); yet, approximately 1,000 subjects received the test drug articaine. Subjects received the lowest effective dose of anesthetic, administered as submucosal infiltration, a nerve block or both. Total dose was not to exceed 7.0 milligrams per kilogram of body weight.

We determined efficacy on a gross scale immediately after the procedure by having both the subject and investigator rate the pain experienced by the subject during the procedure

using a visual analog scale, or VAS, ranging from 0 = "no pain" to 10 = "worst pain imaginable." Because the data did not meet normality assumptions, we used a nonparametric test—Kruskal-Wallis—to analyze the VAS data for the treatment groups. We evaluated safety by measuring vital signs before and after treatment and by assessing adverse events throughout the trial; we did not include the safety findings in this article.

We conducted all of the trials in compliance with good clinical practice guidelines and received

institutional review board (U.S.) or ethics review committee (U.K.) approval before initiating the trials.

## RESULTS

**Demographics.** The demographics of the subjects enrolled and treated in the three trials are summarized in Table 2. We randomized 1,326 patients and treated 1,325: 882 with articaine and 443 with lidocaine. There were no statistically significant differences in the studies between treatment groups ( $P = .05$ ) demographically or in

TABLE 5

## SUMMARY OF VISUAL ANALOG SCALE PAIN SCORES IN ARTICAIN AND LIDOCAINE GROUPS STRATIFIED BY PROCEDURE COMPLEXITY.

PARAMETER	4 PERCENT ARTICAIN WITH EPINEPHRINE 1:100,000		2 PERCENT LIDOCAINE WITH EPINEPHRINE 1:100,000		P VALUE*
	Simple	Complex	Simple	Complex	
<b>Number of Subjects</b>	674	207	338	104	—
<b>Investigator Score (Centimeters)</b>					
Mean	0.3	0.5	0.4	0.6	—
Median	0.0	0.2	0.0	0.2	.965
Range	0 to 9.0	0 to 7.3	0 to 9.0	0 to 6.4	—
<b>Subject Score (cm)</b>					
Mean	0.4	0.6	0.6	0.7	—
Median	0.0	0.2	0.0	0.1	.602
Range	0 to 8.0	0 to 8.7	0 to 9.8	0 to 7.7	—

\*Two-sided *P* value from a Kruskal-Wallis test comparing treatment groups.

the proportion of subjects undergoing simple or complex procedures. Mean ages of subjects in the articaine and lidocaine groups were 36.2 years  $\pm$  0.52 SEM and 36.5 years  $\pm$  0.73 SEM, respectively. We treated 50 subjects 4 to 12 years of age with articaine and 20 subjects 4 to 12 years of age with lidocaine; these subjects represented 5 percent of the study population.

**Drug volume.** We administered as much of the drug as was necessary to achieve adequate anesthesia in the subjects. The average volume of anesthetic administered was comparable between the articaine and lidocaine groups. The mean volume for simple procedures was 2.5 mL  $\pm$  0.07 SEM of articaine or 2.6 mL  $\pm$  0.09 SEM of lidocaine. For complex procedures, the mean volume was

4.2 mL  $\pm$  0.15 SEM of articaine or 4.5 mL  $\pm$  0.21 SEM of lidocaine. Table 3 summarizes drug administration for simple and complex procedures in both treatment groups.

**Procedure duration.** The average duration of both simple and complex dental procedures was comparable between the articaine and lidocaine groups (Table 4). The range of duration was wide: from zero minutes to 220 minutes.

**Pain ratings.** We included in the efficacy analyses all patients who received a study drug and had a VAS evaluation performed. We found no statistical difference between the two treatment groups ( $P = .05$ ) with respect to either subject or investigator ratings of pain using the VAS scoring system. For all groups tested, mean pain scores determined by both patients and investigators were less than 1.0:

0.3 to 0.6 for investigators and 0.4 to 0.7 for subjects (Table 5).

**Safety.** No serious adverse events related to the study medication occurred. Minor adverse events included postprocedural pain, headache, facial edema, infections, gingivitis and transient paresthesia; these events occurred with equal frequency in the articaine and lidocaine groups.

#### DISCUSSION

The efficacy of 4 percent articaine with epinephrine 1:100,000 vs. 2 percent lidocaine with epinephrine 1:100,000 was demonstrated on a gross level in three well-controlled, randomized, double-blind, multicenter trials. A total of 1,325 subjects were treated in these trials, 882 of whom received 4 percent articaine with epinephrine 1:100,000 and 443 of whom received 2 percent lido-

caine with epinephrine 1:100,000. The primary efficacy parameter was the subjective evaluation of pain during the dental procedure, rated by both the subjects and the investigators. VAS assessment of pain provides a gross, but validated and meaningful, measure of anesthetic efficacy, which can be administered to both adults and children. Articaine's anesthetic efficacy was demonstrated by the low mean pain scores in all studies (mean subject and investigator ratings less than 1.0 for both simple and complex dental procedures).

We found no significant differences in VAS pain scores between subjects receiving the articaine with epinephrine and those receiving the lidocaine with epinephrine, either for subject or investigator ratings. We ensured comparability of treatment groups by stratifying according to the type of procedure to be performed. The numbers of subjects treated were sufficient to justify statistical comparisons of efficacy. The use of a 10-centimeter VAS scoring system was expected to reveal any gross difference existing between the two treatments. Since the studies used identical protocols, and the results obtained were comparable, a combined analysis of the trials was valid. These results, given in Table 5, were consistent with the efficacy results for each study individually and demonstrated that there is no difference between 4 percent articaine with epinephrine 1:100,000 and 2 percent lidocaine with epinephrine 1:100,000 when measuring efficacy on a gross scale.

In published studies, articaine with epinephrine has

been shown to be comparable with other local anesthetics with respect to anesthetic efficacy during dental procedures.<sup>6,8,9,11,12</sup> Cowan<sup>12</sup> reported that time to onset (based on subjects' experience of pain during drilling) and duration of anesthesia (sensitivity to probe) after administration of 4 percent articaine with epinephrine 1:200,000 (1.0 mL, maxillary infiltration, n = 57) were comparable with or better than the time to onset and duration of anesthesia for other similar agents.

In a double-blind study by

***We found articaine to be well-tolerated in 882 subjects, and that it provided clinically effective pain relief during most dental procedures.***

Winther and Nathalang,<sup>6</sup> 71 subjects (40 adults, 31 children) undergoing restorative dental treatment received 4 percent articaine with epinephrine 1:200,000 and 4 percent prilocaine with epinephrine 1:200,000 in a randomized, cross-over order for identical treatment of teeth on contralateral sides of the mouth (each side treated in a separate visit; 0.6 mL for maxillary infiltration and 1.8 mL for mandibular for nerve block). There was no significant difference between the two treatments in time to onset or duration of anesthesia as determined by electrical pulp stimulation before and during the procedure.

In other studies in which subjects rated pain during dental procedures, articaine with epinephrine compared favorably to other local anesthetics.<sup>15,16</sup> In a study by Rahn and colleagues,<sup>15</sup> 87 percent (n = 257) of subjects who received 4 percent articaine with epinephrine 1:200,000 rated the anesthetic effect as complete (totally painless) compared with 61 percent (n = 287) of subjects who received 2 percent articaine without epinephrine. In a comparative study conducted by Khoury and colleagues,<sup>16</sup> 73.1 percent of subjects who received 4 percent articaine with epinephrine 1:100,000 (n = 408) and 70.4 percent of subjects who received 4 percent articaine with epinephrine 1:200,000 (n = 382) were pain-free during dental procedures compared with 66.7 percent of subjects who received 2 percent lidocaine with epinephrine 1:100,000 (n = 363) and 56.8 percent of subjects who received 3 percent prilocaine with the vasoconstrictor felypressin (n = 364).

#### CONCLUSIONS

Four percent articaine with epinephrine 1:100,000 is a safe and effective local anesthetic for use in clinical dentistry. In this investigation consisting of three randomized, double-blind trials, we found articaine to be well-tolerated in 882 subjects, and that it provided clinically effective pain relief during most dental procedures. Furthermore, we observed no significant difference in pain relief between subjects in the 4 percent articaine with epinephrine 1:100,000 group and those in the 2 percent lidocaine with epinephrine 1:100,000 group.

For 4 percent articaine with

epinephrine 1:100,000, 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 both adults and children. ■

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For a complete list of the primary investigators in this study, contact the corresponding author.

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