

Articaine hydrochloride: a study of the safety of a new amide local anesthetic

STANLEY F. MALAMED, D.D.S.; SUZANNE GAGNON, M.D.; DOMINIQUE LEBLANC, D.Pharm.

Local anesthesia forms the backbone of pain control techniques in dentistry. From cocaine (1884) to procaine (1904) to lidocaine (1948), dentistry has been in the forefront in seeking to provide patients with pain-free care. As effective as these drugs are, however, research has continued to seek safer and more effective local anesthetics.

Articaine hydrochloride is an amide local anesthetic, 4-methyl-3[2-(propyl-amino) propionamido]-2-thiophenecarboxylic acid, methyl ester hydrochloride. It was synthesized in 1969 in Germany, where it entered clinical use in 1976; in April 2000, the U.S. Food and Drug Administration granted approval for the sale of 4 percent articaine with 1:100,000 epinephrine in the United States under the name of Septocaine (Septodont).

Articaine is unique among amide local anesthetics in that it contains a thiophene group, which increases its liposolubility, and is the only widely used amide local anesthetic that also contains an ester group. The ester group enables articaine to undergo biotransformation in the plasma (hydrolysis by plasma esterase) as well as in the liver (by hepatic microsomal enzymes). The primary metabolite, articainic acid, is inactive.¹ Articaine and its metabolites are eliminated via the kidneys. Approximately 5 percent to 10 percent of articaine is excreted unchanged.²

Articaine reversibly blocks nerve conduction through a mechanism of action similar to that of other amide

Background. Articaine is an amide local anesthetic introduced clinically in Germany in 1976 and subsequently throughout Europe, Canada and, in 2000, the United States.

Methods. The authors report on three identical single-dose, randomized, double-blind, parallel-group, active-controlled multicenter studies that were conducted to compare the safety and efficacy of articaine (4 percent with epinephrine 1:100,000) with that of lidocaine (2 percent with epinephrine 1:100,000).

Results. A total of 1,325 subjects participated in these studies, 882 of whom received articaine 4 percent with epinephrine 1:100,000 and 443 of whom received lidocaine 2 percent with epinephrine 1:100,000. The overall incidence of adverse events in the combined studies was 22 percent for the articaine group and 20 percent for the lidocaine group. The most frequently reported adverse events in the articaine group, excluding postprocedural dental pain, were headache (4 percent), facial edema, infection, gingivitis and paresthesia (1 percent each). The incidence of these events was similar to that reported for subjects who received lidocaine. The adverse events most frequently reported as related to articaine use were paresthesia (0.9 percent), hypesthesia (0.7 percent), headache (0.55 percent), infection (0.45 percent), and rash and pain (0.3 percent each).

Conclusions. Articaine is a well-tolerated, safe and effective local anesthetic for use in clinical dentistry.

local anesthetics. Epinephrine is included in the clinical formulation both to retard absorption of articaine, thereby prolonging the duration of clinically adequate anesthesia, and to minimize systemic absorption of the active drug.

Articaine is used clinically as a 4 percent solution with epinephrine 1:100,000 or 1:200,000. The onset of anesthesia with articaine 4 percent with epinephrine 1:200,000 is 1.5 to 1.8 minutes for maxillary infiltration and 1.4 to 3.6 minutes for inferior alve-

olar nerve block.^{3,4} The duration of soft-tissue anesthesia is 2.25 hours for maxillary infiltration and approximately four hours for nerve block.⁴ 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.⁵

This article reports the results of a three-study clinical program designed to compare the safety and efficacy of articaine 4 percent with epinephrine 1:100,000 with that of lidocaine 2 percent with epinephrine 1:100,000. An earlier article in JADA reported the study's results regarding the efficacy of articaine.⁶

METHODS

Three identical single-dose, randomized, double-blind, parallel-group, active-controlled multicenter studies were conducted to compare the safety and efficacy of articaine (4 percent with epinephrine 1:100,000) with that of lidocaine (2 percent with epinephrine 1:100,000). The studies were conducted at a total of 27 sites (eight in Great Britain, 19 in the United States).

At each site, subjects 4 to 80 years of age undergoing general dental procedures were stratified according to the complexity of the procedure being performed:

- simple—single extractions with no complications, routine operative procedures, single apical resections and single-crown procedures;
- complex—multiple extractions, multiple-crown and/or bridge procedures, multiple apical resections, alveolectomies, mucogingival operations and other osseous surgical procedures.

Exclusion criteria included the following: pregnancy; bony, fully impacted teeth or maxillofacial surgery; known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any ingredients in the anesthetic solutions; concomitant cardiac or neurologic disease; a history of 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); an expectation of requiring nitrous oxide or any topical or general anesthetic (top-

ical anesthetic was allowed in the British study); or subjects who had taken aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs or other analgesic agents within 24 hours before administration of the study medication.

Within each stratum, subjects were randomized in a 2:1 ratio to receive articaine or lidocaine (so as to gather more data on the test drug, articaine). Both formulations contained epinephrine 1:100,000. Patients received the lowest effective dose of anesthesia, to be administered as submucosal infiltration and/or nerve block. Total dose was not to exceed 7.0 milligrams per kilogram of body weight.

Safety evaluations included vital signs obtained before and after administration of the anesthetic and assessment of adverse events during the treatment visit. Additionally, reports of adverse events were elicited during telephone follow-up at 24 hours and seven days after the procedure. Subjects were questioned specifically regarding the presence of persistent numbness and/or tingling of the mouth or face (a condition called paresthesia).

The numbers of subjects enrolled and treated in the three trials are summarized in Table 1. All studies were conducted in compliance with good clinical practice guidelines and received approval from, as appropriate, ethics review committees (in Great Britain) or institutional review boards (in the United States).

RESULTS

Subject demographics. A total of 1,325 patients were treated, 882 in the articaine group and 443 in the lidocaine group. There were no statistically significant differences in the studies between the articaine and lidocaine treatment groups with respect to age, sex, weight, race distribution or the proportion of subjects undergoing simple or complex procedures. Mean ages of subjects in the articaine and lidocaine groups were 36.2 and 36.5 years, respectively. Fifty subjects younger than age 13 years were treated in the articaine group, and 20 subjects younger than age 13 years were treated in the lidocaine group, representing 5 percent of the study population. Table 1 summarizes patient demographics for each group.

Drug volumes. Patients were administered

.....
The anesthetic activity of articaine/epinephrine combinations has been demonstrated to be comparable to that of other anesthetic combinations.

TABLE 1

PATIENT DEMOGRAPHICS.			
SUBJECT VARIABLE	TREATMENT GROUP		TOTAL
	Articaine 4% With Epinephrine 1:100,000	Lidocaine 2% With Epinephrine 1:100,000	
Total Treated Subjects (n)	882	443	1,325
Age in Years (n [%])			
4 to < 13	50 (6)	20 (5)	70 (5)
13 to < 65	778 (88)	396 (89)	1174 (89)
65 to < 75	43 (5)	23 (5)	66 (5)
≥ 75	11 (1)	4 (1)	15 (1)
Mean ± SEM*	36.2 ± 0.52	36.5 ± 0.73	36.3 ± 0.42
Weight (Kilograms)			
Mean ± SEM	72.3 ± 0.62 (n = 879)	70.9 ± 0.86 (n = 438)	71.9 ± 0.51 (n = 1,317)
Sex (n [%])			
Female	464 (53)	259 (58)	723 (55)
Male	418 (47)	184 (42)	602 (45)
Race (n [%])			
White	647 (73)	330 (74)	977 (74)
African-American	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 the mean.			

as much of the study drug as was necessary to achieve adequate anesthesia. The average volume of anesthetic administered was comparable for the articaine and lidocaine groups. Table 2 summarizes drug administration for simple and complex procedures in both treatment groups.

Duration of procedures. The average duration of both simple and complex dental procedures was comparable between the articaine and lidocaine groups (Table 2). The range of duration was wide, from one minute to more than three and one-half hours.

Adverse events. Adverse events were determined in telephone interviews conducted by the primary investigators with the patient at 24 hours and seven days after treatment. Therefore, the vast majority of these events are related by patients and are alleged as opposed to confirmed.

In the articaine group, 191 of 882 patients (22 percent) reported at least one adverse event. In the lidocaine group, 89 of 443 patients (20 percent) reported at least one adverse event. One patient in the articaine group had an adverse event reported as serious but unrelated to the study medication (squamous cell carcinoma). One patient in the lidocaine group discontinued participation in the study owing to chest pain and dizziness, considered to be possibly related to the study medication. No deaths were associated with these studies.

In the articaine group (n = 882), the most common adverse event was postprocedural pain (13 percent), followed by headache (4 percent). Facial edema, infection, gingivitis and paresthesia each was reported by 1 percent of patients. All other adverse events each were reported by less than 1 percent of patients.

TABLE 2

STUDY DRUG ADMINISTRATION: COMPARISON OF ARTICAIN 4% WITH EPINEPHRINE 1:100,000 TO LIDOCAINE 2% WITH EPINEPHRINE 1:100,000.

VARIABLE	DRUG ADMINISTERED AND TYPE OF PROCEDURE			
	Articaine 4% With Epinephrine 1:100,000		Lidocaine 2% With Epinephrine 1:100,000	
	Simple*	Complex [†]	Simple	Complex
Volume and dose of anesthetic				
Subjects (n)	675	207	338	104 [‡]
Mean volume ± SEM [§] (mL ^{**})	2.5 ± 0.07	4.2 ± 0.15	2.6 ± 0.09	4.5 ± 0.21
Mean dose ± SEM (mg/kg ^{††})	1.48 ± 0.042	2.36 ± 0.094	0.80 ± 0.031	1.26 ± 0.065
Duration of procedure				
Subjects (n)	675 [‡]	207	338 ^{‡‡}	105 [‡]
Mean duration (minutes)	36.4 ± 1.28	58.3 ± 3.07	37.7 ± 2.01	52.6 ± 3.99
Range (minutes)	0-217	1-215	0-220	1-171
* Simple procedures were defined as single extractions with no complications, routine operative procedures, single apical resections and single-crown procedures. † Complex procedures were defined as multiple extractions, multiple-crown and/or bridge procedures, multiple apical resections, alveolectomies, mucogingival operations and other osseous surgical procedures. ‡ Missing data for one patient. § SEM: Standard error of the mean. ** mL: Milliliter. †† mg/kg: Milligrams per kilogram of body weight. ‡‡ Missing data for two patients.				

The incidence of adverse events in the lidocaine group (n = 443) was similar, with postprocedural pain reported most frequently (12 percent), followed by headache (3 percent). Facial edema, gingivitis and hypesthesia each was reported by 1 percent of patients in the lidocaine group; all other adverse events each were reported by less than 1 percent of patients.

The total number of adverse events reported by 1 percent or more of patients in either study group are summarized in Table 3. The incidence of adverse events was not greatly affected by race, sex or age, although patients aged 4 to 12 years tended to report fewer adverse events.

The incidence of adverse events was higher in Great Britain (42 percent of patients in both articaine and lidocaine treatment groups) than in the United States (17 percent of patients in the articaine group and 15 percent of patients in the lidocaine group). The disparity is due to the higher reporting rate of postprocedural pain as an adverse event in Great Britain than in the United

States (34 percent for articaine patients in Great Britain as compared with 8 percent for articaine patients in the United States).

Drug-related adverse events. Of the 882 patients in the articaine group, 37 (4 percent) had adverse events considered by the investigator to be related to the study medication, compared with 16 of the 443 patients (4 percent) in the lidocaine group (Table 4). For both treatment groups, each adverse event considered to be related to the study medication was reported by less than 1 percent of patients. In the articaine group, the most commonly reported drug-related adverse events were paresthesia (0.9 percent), hypesthesia (0.7 percent), headache (0.55 percent), infection (0.45 percent), rash (0.3 percent) and pain (0.3 percent). In the lidocaine group, the most common drug-related adverse events were headache (0.7 percent), rash (0.7 percent), paresthesia (0.45 percent) and dizziness (0.45 percent).

Accidental lip injury was the only adverse event considered by investigators to be related to

TABLE 3

ADVERSE EVENTS REPORTED BY 1 PERCENT OR MORE OF PATIENTS IN EITHER TREATMENT GROUP.*		
BODY SYSTEM/ADVERSE EVENT	TREATMENT GROUP (n [%])	
	Articaine 4% With Epinephrine 1:100,000 (n = 882)	Lidocaine 2% With Epinephrine 1:100,000 (n = 443)
Body as a Whole		
Face edema	13 (1)	6 (1)
Headache	31 (4)	15 (3)
Infection	10 (1)	3 (< 1)
Pain	114 (13)	54 (12)
Oral System		
Gingivitis	13 (1)	5 (1)
Nervous System		
Hypesthesia	7 (< 1)	5 (1)
Paresthesia	11 (1)	2 (< 1)

* Report of all adverse events, regardless of whether they were drug-related.

the study drug among patients 4 to 12 years of age. The occurrence of drug-related adverse events among all subjects is similar across demographic subgroups of age, race, sex and dose.

All study drug-related adverse events were mild to moderate in intensity, except for one case of infection and one case of mouth ulceration, each of which was rated as severe in intensity. Both events occurred in the articaine group in white males between 13 and 64 years of age.

Vital signs. Supine systolic and diastolic blood pressures were measured before the study drug was administered and at one and five minutes postadministration and postprocedure. Mean supine blood pressure values changed very little, decreasing slightly from baseline at all time points after administration of the study drug. These changes were not clinically significant, and there were no statistically significant differences in mean supine blood pressure between treatment groups.

Mean standing systolic and diastolic blood pressures, obtained before and after the procedure, also changed very little from baseline

values, with mean standing systolic blood pressure very slightly increased and mean standing diastolic blood pressure very slightly decreased from baseline values after the procedure. These changes were not clinically significant, and there were no statistically significant differences in mean standing blood pressure between treatment groups.

Heart rate and respiratory rates were measured before the study drug was administered, at one and five minutes postadministration, and after the procedure. For both heart rate and respiratory rate, mean values increased slightly at one and five minutes, but by the postprocedure measurement point, mean values had decreased slightly below baseline values. The changes from baseline were not statistically or clinically significant, and there were no statistically significant differences between treatment groups.

DISCUSSION

The overall incidence of adverse events in the combined studies was 22 percent in the articaine group and 20 percent in the lidocaine group. The most frequently reported adverse events in the

All study drug-related adverse events were mild to moderate in intensity, except for one case of infection and one case of mouth ulceration, each of which was rated as severe in intensity.

TABLE 4

ADVERSE EVENTS CONSIDERED BY PRIMARY INVESTIGATORS TO BE RELATED TO STUDY MEDICATION.

BODY SYSTEM/ADVERSE EVENT	INCIDENCE BY TREATMENT GROUP (n [%])	
	Articaine 4% With Epinephrine 1:100,000 (n = 882)	Lidocaine 2% With Epinephrine 1:100,000 (n = 443)
Subjects With at Least One Related Adverse Event Related to Study Medication (n [%])	37 (4)	16 (4)
Body as a Whole		
Infection	4 (0.45)	1 (0.2)
Headache	5 (0.55)	3 (0.6)
Pain	3 (0.3)	0
Injection site pain	1 (0.1)	1 (0.2)
Accidental injury*	1 (0.1)	0
Back pain	1 (0.1)	0
Abdominal pain	1 (0.1)	1 (0.2)
Asthenia	1 (0.1)	1 (0.2)
Malaise	1 (0.1)	0
Chest pain	0	1 (0.2)
Chills	0	1
Cardiovascular System		
Tachycardia	1 (0.1)	0
Digestive System		
Vomiting	0	1 (0.2)
Constipation	1 (0.1)	0
Diarrhea	2 (0.2)	0
Dyspepsia	1 (0.1)	0
Nausea	1 (0.1)	0
Stomatitis	1 (0.1)	0
Metabolic and Nutritional System		
Thirst	1 (0.1)	0
Musculoskeletal System		
Arthralgia	0	1 (0.2)
Myalgia	0	1 (0.2)
Nervous System		
Paresthesia	8 (0.9)	2 (0.45)
Hypesthesia	6 (0.7)	1 (0.2)
Dizziness	1 (0.1)	2 (0.45)
Dry mouth	1 (0.1)	0
Increased salivation	1 (0.1)	0
Neuropathy	1 (0.1)	0
Somnolence	1 (0.1)	0
Circumoral paresthesia	0	1 (0.2)
Neuralgia	0	1 (0.2)
Oral System		
Mouth ulceration	1 (0.1)	0
Skin and Appendages		
Pruritis	2 (0.2)	1 (0.2)
Rash	0	3 (0.6)
Sweating	0	1 (0.2)
Special Senses		
Ear pain	3 (0.3)	0
Taste perversion	1 (0.1)	0

* Lip injury in a subject younger than 13 years of age.

articaine group, excluding postprocedural dental pain, were headache (4 percent), facial edema, gingivitis, paresthesia/hypesthesia and infection (1 percent each). The incidence of these events was similar in the lidocaine group. Adverse events most frequently reported as drug-related in the articaine group were paresthesia (0.9 percent), hypesthesia (0.7 percent), headache (0.55 percent), infection (0.45 percent), rash (0.3 percent) and pain (0.3 percent). Among the 50 children (aged 4 to 12 years) who received articaine in these studies, one adverse event (lip injury) was considered related to treatment.

Haas and Lennon⁷ published a retrospective analysis of paresthesia after local anesthetic administration for nonsurgical dental procedures over a 21-year period. Paresthesia was defined as numbness or tingling of the mouth or face. The analysis revealed a higher-than-expected frequency of paresthesia with articaine, based on the number of cartridges used (2.27 per 1 million injections vs. an expected frequency of 1.20 per 1 million injections).

Because of the Haas and Lennon⁷ report, an attempt was made in these studies to obtain data regarding paresthesia after injection. During telephone follow-up 24 hours and seven days after the procedure, and using the Haas and Lennon definition of paresthesia, researchers specifically asked subjects if they had any ongoing numbness or tingling of the mouth or face. The total number of subjects who reported these symptoms four to eight days after the procedure was eight (1 percent) for the articaine group and five (1 percent) for the lidocaine group. Although more articaine patients than lidocaine patients were believed by investigators to have drug-related symptoms, in five cases (four with articaine, one with lidocaine), the symptoms did not begin on the day of study drug administration, suggesting that they were caused by the procedure rather than the anesthetic. In cases for which resolution dates were available, we determined that the duration of these events was less than one day to 18 days after the procedure. In all cases, the paresthesia ultimately resolved.

Minor fluctuations in vital signs are common during administration of local anesthetic. There

were no consistent changes in vital signs observed at one and five minutes after injection or at the end of the dental procedure. Transient increases and decreases in blood pressure, heart rate and respiratory rate were observed, but they were not clinically significant, and neither were the changes statistically significant between treatment groups. Analysis of combined data for these studies did not indicate any trends in vital signs related to age or sex among subjects receiving articaine. Tachycardia was reported as an adverse event in one subject who received articaine. Anxiety regarding the injection itself or the impending dental procedure may contribute to transient alterations in vital signs.

In a study by Hidding and Khoury,⁸ which evaluated the safety of four commonly used dental anesthetics administered via nerve block techniques in 1,518 adults, 2.6 percent of all subjects had an increase in blood pressure equal to or greater than 20 millimeters of mercury, or mm Hg, and 7.4 percent had a drop in blood pressure equal to or greater than 20 mm Hg at two minutes after injection. Increases in heart rate of more than 20 beats per minute were observed in 4.2 percent of subjects. Vital sign changes in our studies, thus, were well within those expected with the use of dental anesthetics.

The immunogenic potential of articaine is very low. Historical experiences indicate that allergic reactions resulting from sensitivity to articaine are rare. However, articaine solutions with epinephrine contain an antioxidant, sodium bisulfite, which can cause allergic-type reactions. In addition, some commercially available forms of articaine with epinephrine (although not the study drug) also contain the antibacterial preservative methylparaben, which may have contributed to allergic reactions reported with articaine.⁹ Allergic-type reactions that have been reported with articaine include edema, urticaria, erythema and anaphylactic shock. In the three studies discussed here, reports of rash or pruritis were no more frequent with articaine (n = 2) than with lidocaine (n = 4), and no serious allergic reactions were seen in either treatment group. Patients allergic to articaine likely would be allergic to lidocaine and the other amide local anesthetics.

The most frequently reported adverse events in the articaine group, excluding postprocedural dental pain, were headache (4 percent), facial edema, gingivitis, paresthesia/hypesthesia and infection (1 percent each).

Published data support the overall safety and tolerance of articaine with epinephrine. In a prospective, randomized, double-blind comparison of articaine 4 percent with epinephrine 1:200,000 (n = 383), articaine 4 percent with epinephrine 1:100,000 (n = 408), prilocaine 3 percent with felypressin 1:1,185,000 (n = 364), and lidocaine 2 percent with epinephrine 1:100,000 (n = 363) administered via nerve block technique, there was no difference among the four groups with respect to effects on blood pressure and heart rate.^{8,10} The most frequent postoperative complaint, headache, was observed with similar frequency (15 percent to 22 percent) in all treatment groups. One subject who received articaine 4 percent with epinephrine 1:100,000 experienced diplopia after injection; it resolved after 15 minutes. Reviews of clinical experience with articaine 4 percent with epinephrine 1:200,000 reported no local reactions or secondary effects in 500 injections¹¹ (1.8 milliliters) and 7,500 injections¹² (1.0 to 3.6 mL). Evaluation of 84 subjects who received articaine 4 percent with epinephrine 1:100,000 (0.3 to 4.5 mL) revealed postsurgical complications of mucosal ulcerations, localized osteitis and sharp pain.¹³

Methemoglobinemia has been shown to develop with some types of local anesthetics. Clinical tests of articaine, bupivacaine and etidocaine administered as central nerve block anesthetic for urological procedures (n = 103) indicated no elevation of methemoglobin with articaine.¹⁴

CONCLUSIONS

Articaine 4 percent with epinephrine 1:100,000 is a safe local anesthetic for use in clinical dentistry. Articaine can be used effectively in both adults and children. Articaine was well-tolerated in 882 subjects who received the drug in these clinical trials and had a toxicity profile comparable to that of lidocaine. Dentistry's clinical experience with articaine/epinephrine formulations through the years supports the assertion that the risk of systemic toxicity with articaine is low. Articaine with epinephrine is contraindicated in patients with known sensitivity to amide-type local anesthetics and in patients with sulfite sensitivity (such as some people with allergic-type asthma). Articaine should be used with caution in patients

Dentistry's clinical experience with articaine/epinephrine formulations through the years supports the assertion that the risk of systemic toxicity with articaine is low.

with hepatic disease and significant impairments in cardiovascular function—both of which conditions place patients in the American Society of Anesthesiologists classification of ASA IV (having severe systemic disease that is a constant threat to life)—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 younger than 4 years of age is not recommended, since no data exist to support such usage.

The use of articaine with epinephrine for local anesthesia is well-established in clinical dental practice in continental Europe and Canada, with more than 100 million cartridges having been sold. Articaine 4 percent with epinephrine 1:100,000 provides effective anesthesia with a low risk of toxicity that appears comparable to that of other local anesthetics. ■

Dr. Malamed is a professor of anesthesia and medicine, DEN 4302, School of Dentistry, University of Southern California, 925 W. 34th St., Los Angeles, Calif. 90089-0641, e-mail "malamed@hsc.usc.edu". Address reprint requests to Dr. Malamed.

Dr. Gagnon is vice president, Medical Affairs, Omnicare Clinical Research, Blue Bell, Pa.

Dr. Leblanc is scientific director, Spécialités Septodont, Saint-Maur des Fossés Cedex, France.

The authors would like to thank Spécialités Septodont, the manufacturer of the drug products used in the three trials discussed in this article, for providing materials and funding.

A complete list of the primary investigators in this study is available from Dr. Malamed.

1. van Oss GE, Vree TB, Baars AM, Termond EF, Booij LH. Pharmacokinetics, metabolism, and renal excretion of articaine and its metabolite articainic acid in patients after epidural administration. *Eur J Anaesthesiol* 1989;6(1):49-56.
2. Vree TB, Baars AM, van Oss GE, Booij LH. High performance liquid chromatography and preliminary pharmacokinetics of articaine and its 2-carboxy metabolite in human serum and urine. *J Chromatogr* 1988;424(2):440-4.
3. Donaldson D, James-Perdok L, Craig BJ, Derkson GD, Richardson AS. A comparison of Ultracaine DS (articaine HCl) and Citanest Forte (prilocaine HCl) in maxillary infiltration and mandibular nerve block. *J Can Dent Assoc* 1987;53(1):38-42.
4. Cowan A. Clinical assessment of a new local anesthetic agent: articaine. *Oral Surg Oral Med Oral Pathol* 1977;43:174-80.
5. Lemay H, Albert G, Helie P, et al. Ultracaine in conventional operative dentistry. *J Can Dent Assoc* 1984;50:703-8.
6. Malamed SF, Gagnon S, Leblanc D. Efficacy of articaine: a new amide local anesthetic. *JADA* 2000;131(5):635-42.
7. Haas DA, Lennon D. A 21 year retrospective study of reports of paresthesia following local anesthetic administration. *J Can Dent Assoc* 1995;61(4):319-20.
8. Hidding J, Khoury F. General complications in dental local anesthesia. *Dtsch Zahnarztl Z* 1991;46(12):831-6.
9. MacColl S, Young ER. An allergic reaction following injection of

local anesthetic: case report. *J Can Dent Assoc* 1989; 55(12):981-4.

10. Khoury F, Hinterthan A, Schurmann J, Arns H. Clinical comparative study of local anesthetics: random double blind study with four commercial preparations. *Dtsch Zahnärztl Z* 1991;46(12):822-4.

11. Freyman L, Klewansky P. L'Alphacaine N: un nouvel anesthésique loco-régional en odontologie. *L'Information Dentaire* 1981;32:3003-5.

12. Eifinger FF, Stratmann KR. Nouveaux aspects de l'anesthésie locale en dentisterie conservatrice. *Schweizerische Monatsschrift für*

Zahnheilkunde 1981;91(1):1-7.

13. David J. A propos d'un nouvel anesthésique: l'Alphacaine SP en pratique courante—a propos de 80 cas. *L'Information Dentaire* 1984;16(4):1589-94.

14. Rupieper N, Stocker L. Met-Hb formation and local anesthesia using bupivacaine, articaine and etidocaine. *Anaesthetist* 1981;30(5):23-5.