CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-971

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,971 **Submission Date:** March 30, 1998
June 30, 1998

Drug Name and Formulation: Septanest — nd Septanest — (articaine) solution for injection, 4% articaine hydrochloride with epinephrine 1/200,000 and 1/100,000 solution for injection

Sponsor: Deproco, Inc., New Castle, DE 19720 (Manufacturer: Specialties Septodont, France)

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: New Drug Application, NME, 1S

SYNOPSIS: Septanest — — solutions for injection contain 4% articaine along with epinephrine 1/200,000 and 1/100,000 solution respectively. Articaine hydrochloride is an amide-type local anesthetic that has a reversible effect of blocking the conduction of painful sensations. Articaine has structural features similar to several local anesthetics, with an additional ester group (like tetracaine) for easy hydrolysis by plasma esterases. Epinephrine is a vasoconstrictor added to articaine to slow down its passage into the general circulation and thus ensure the prolonged maintenance of active tissue concentration of articaine. This is indicated for infiltration anesthesia and nerve block anesthesia in clinical dentistry in patients 4 years and older. The recommended dose depends on the indication and should not exceed 7 mg/kg body weight.

PHARMACOKINETIC / BIOAVAILABILITY STUDIES

This NDA contains several clinical and few pharmacokinetic studies along with literature reports. The formulation used throughout the drug development program in the U.S. (U.S. clinical and PK studies) is the same as the to-be marketed formulation. Supportive clinical studies (e.g. conducted in France) utilized a slightly different formulation. Articaine has been extensively used in Canada and Europe where this product is marketed. Data is available as several literature reports. Therefore, based on FDA's recommendation, the sponsor agreed to summarize the pharmacokinetics in the NDA. to support the literature data. . Published literature has been submitted which includes pharmacokinetics in pediatric population. However, the literature utilizes formulations that are likely to be different than the one currently proposed. The pharmacokinetic data indicates that this drug is rapidly absorbed (Tmax = 0.4 to 0.8 hours) and highly metabolized, likely by plasma esterases, to mainly articainic acid (an inactive metabolite). Articainic acid plasma levels were 4 to 6 fold higher than articaine. Articaine has a relatively rapid onset of action (3.65 $\pm$ 0.39 minutes) and moderate duration of action (68.20 $\pm$ 8.3 minutes). In vitro metabolism studies indicate that metabolism via cytochrome P450 isoenzymes is a minor pathway. Since this drug is highly prone to ester hydrolysis, plasma samples have to be stabilized by esterase inhibitors like sodium or potassium fluoride. Protein binding of articaine is >80%. Adequate assay

validation data for articaine and articainic acid have been submitted by the sponsor. No PK studies have been carried out using the 4% articaine/1:100,000 epinephrine. However, it can be expected that the systemic levels of articaine will be less than those achieved with the lower epinephrine concentration product.

RECOMMENDATION: The present submission (NDA 20-971) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The submission is acceptable provided that a) labeling comments # 1 to 7 and b) comment to sponsor # 1 are adequately addressed by the sponsor.

Please forward comments # 1 to 3 and the labeling comments # 1 to 7 to the sponsor.

TABLE OF CONTENTS:

I. BACKGROUND

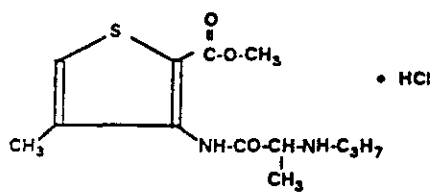
Septanest— are sterile aqueous solutions containing 4% articaine with 1:200,000 or 1:100,000 epinephrine tartrate. Articaine is an amide-type local anesthetic with an

ester group prone to ester hydrolysis. This product is currently used in France, Belgium, Holland, Germany, Spain, Switzerland, Canada, Russia and Italy.

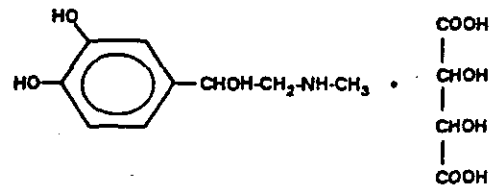
Articaine has the reversible effect of blocking the conduction of painful sensations. Its mechanism of action is to decrease nerve conduction by diminishing the sodium ion influx during the action potential period. It is combined with epinephrine to reduce the systemic absorption of articaine and prolong the duration of local anesthesia. Articaine is indicated for infiltration anesthesia and nerve block anesthesia in clinical dentistry. The recommended total dose ranges from 20 mg (0.5 ml) and not to exceed 204 mg articaine (5.1 ml).

STRUCTURE OF DRUG ENTITY: Articaine is chemically 4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride (a racemic mixture) with a molecular weight of 320.84. Epinephrine bitartrate is chemically (-)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (+) tartrate (1:1 salt) with a molecular weight of 333.3. The structures of articaine and epinephrine are shown below.

ARTICAINE



EPINEPHRINE



II. FORMULATION: The composition of the two formulations of articaine, Septanest™ and Septanest ™' are shown below:

SEPTANEST™ AND SEPTANEST ™ FORMULATION COMPOSITION

INGREDIENT		SEPTANEST ™ (1:100,000 epinephrine)
Articaine hydrochloride		4.000 g
Epinephrine base		0.001 g*
Sodium metabisulphite		0.050g
Sodium chloride		0.160 g
Sodium hydroxide solution q.s.		to pH 5.0 ± 0.2
Water for injection q.s. ad		
* in the form of tartrate		

III. PHARMACOKINETICS AND BIOAVAILABILITY:

The summary of pharmacokinetics of articaine and its metabolite articainic acid are provided here.

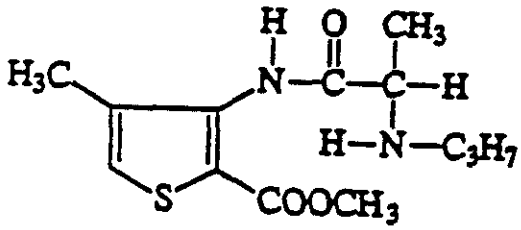
a. ABSORPTION: Following maxillary infiltration of two doses of 1.7 ml and 5.1 ml of Septanest – (4% articaine/1:200,000 epinephrine) in healthy volunteers, articaine was absorbed rapidly. The mean T_{max} across the dose range was 0.4 and 0.8 hours. Mean C_{max} of articaine and its major metabolite articainic acid following the 68 mg dose was 385 ng/ml and 1429 ng/ml and that following the 204 mg dose was 899 ng/ml and 3793 ng/ml. Mean $AUC_{0-\infty}$ of articaine and its major metabolite articainic acid following the 68 mg dose was 631 ng.hr/ml and 3751 ng.hr/ml and that following the 204 mg dose was 1542 ng.hr/ml and 11,543 ng.hr/ml. This data indicates that there is dose proportionality in the pharmacokinetics of articaine and articainic acid, although data from at least 3 doses is necessary to accurately make this statement. Epinephrine PK were not evaluated in this NDA. However, considering the low doses of epinephrine administered, only low concentrations of epinephrine are likely to occur which may be undetectable.

b. DISTRIBUTION: The volume of distribution is about 4.5 L/kg for articaine and 0.6 L/kg for articainic acid (assuming complete conversion of articaine to articainic acid).
Plasma protein binding: In vitro protein binding studies indicate that articaine is about 80% bound to albumin with minor binding to γ-globulin.

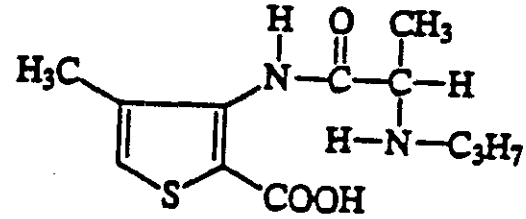
c. ELIMINATION (METABOLISM AND EXCRETION):
Terminal phase half-life: Half-life of articaine is approximately 1.6 to 1.8 hours in healthy volunteers. Elimination half-life of articainic acid is similar to articaine. Mean Cl/F was found to be about 2000 ml/min for articaine.
Metabolism: Articaine is rapidly and extensively metabolized to articainic acid, possibly by plasma carboxyesterases (see the structures below for articaine and articainic acid). In order to stabilize these moieties in plasma, an esterase inhibitor, sodium or potassium fluoride was necessary.

In vitro metabolism studies in human lymphoblastoid systems containing specific CYP isozymes indicate that in vitro metabolism via CYP isozymes constitutes about 5 to 10% of the metabolism of articaine and is a minor metabolic pathway. This metabolism, however, indicates that articainic acid is the primary metabolite formed in liver microsomes.
Excretion: No mass balance study has been conducted with Septanest. However, literature data indicates that about 90% of radioactivity (of articaine dose) is excreted in urine after I.V. administration. Data from this NDA indicates that about 50% of the articaine dose is excreted in urine (mostly as articainic acid) within 24 hours. Only about 2% of the dose is excreted as unchanged articaine in urine. Literature also indicates that articainic acid glucuronide is one of the metabolites excreted in urine. Renal clearance of articaine was found to be 36.3 ml/min after the 68 mg dose and 50.2 ml/min after the 204 mg dose; and that of articainic acid was 175.6 ml/min after the 68 mg dose and 160.6 ml/min after the 204 mg dose.

ARTICAINE



ARTICAINIC ACID



d. SPECIAL POPULATIONS:

Age: The pharmacokinetics of articaine were not evaluated in elderly patients. A literature article was submitted to evaluate the PK of articaine in children of age 3 to 12 years old. Peak levels achieved, according to the sponsor, were comparable to the data obtained in adults (children dosed after adjustment for body weight). However, this data was obtained using a different formulation of articaine and the study itself was not designed appropriately to characterize the articaine pharmacokinetics in children. Hence, this data is insufficient to utilize it for labeling purposes.

Gender: The single and multiple dose PK study conducted in this NDA was carried out in both males and females. Analysis of the PK data for articaine and articainic acid in males and females indicated no statistically significant differences in any parameters except the renal clearance after the 68 mg dose. Renal clearance in males was found to be 28.3 ml/min and that in females was found to be 45.2 ml/min. Since such a difference was not reflected in the plasma concentrations and since renal elimination of unchanged articaine is only a minor pathway, this difference may not be clinically significant. However, this trend should be compared to the safety data from pivotal clinical trials.

V. PHARMACODYNAMICS: Following a single dose injection of 1.7 ml of 4% articaine hydrochloride with 1:200,000 epinephrine, the mean time to onset of anesthesia (time to lack of perception at maximum stimulation with a pulp stimulator) was 3.65 ± 0.39 minutes. The mean duration of anesthesia (time from onset of anesthesia to decrease from maximum stimulation by 50%) was 68.20 ± 8.3 minutes.

VI. ANALYTICAL METHODS VALIDATION: Articaine and articainic acid were measured in human plasma and urine by [redacted] These assays were adequately validated. Adequate information regarding stability of samples in human plasma [redacted] has been provided. Further, assay performance within each study has also been submitted.

COMMENTS TO THE MEDICAL OFFICER (NOT TO BE SENT TO THE SPONSOR):

a. No pharmacokinetic data has been submitted using the high strength epinephrine/articaine product. However, the articaine plasma concentrations achieved with the 4% articaine/1:200,000 epinephrine are likely to be higher. Therefore, the product evaluated provides the most information regarding systemic toxicity.

b. A significant gender effect on the renal clearance of articaine was found only after the 68 mg dose, and not after the 204 mg dose. However, no statistically significant gender effect was seen on other PK parameters of articaine and articainic acid. While, this may not be of major importance, since articaine is extensively metabolized to inactive articainic acid, we would request you to carefully evaluate if there are any gender differences in clinical safety of articaine.

COMMENTS TO THE SPONSOR:

1) An attempt should be made to identify the esterases involved in the metabolism of articaine and also to provide any information available with respect to the disease states which might lead to insufficient esterases. This is important to characterize any subpopulations where caution may be necessary re: systemic toxicities.
2) While important protein binding information has been currently submitted, in future, protein binding studies should also be conducted in plasma in order to characterize the total protein binding, in addition to specific proteins as done in this NDA.
3) Similarly, total metabolism in in vitro human liver microsomes should also be determined in addition to specific isozymes that metabolize the drug.

LABELING COMMENTS:

1. Under the DESCRIPTION section of the label, please include the pH of the Septanest — and Septanest— formulations.
2. Under the Pharmacokinetics – absorption section, please include the peak plasma levels of articaine and articainic acid achieved after both the 68 and 204 mg doses of articaine. In addition, modify the existing paragraph to replace the word [redacted] with Articaine to read "Articaine reaches peak plasma concentration about 25 minutes after a single dose injection and 48 minutes after three doses."
3. Under the Pharmacokinetics - metabolism section, it should be mentioned that articainic acid glucuronide is also a possible metabolite of articaine that is excreted in urine. Also, it should be mentioned that articainic acid is an inactive metabolite.
4. Under the Pharmacokinetics – excretion section, please remove the entire paragraph and replace it with : *The elimination half life of articaine is about 1.8 hours and that of articainic acid is about 1.5 hours. Articaine is excreted primarily through urine with 53 – 57% of the administered dose eliminated in the first 24 hours following submucosal*

administration. Articainic acid is the primary metabolite in urine.

5. Under the Pharmacokinetics – special population – geriatric section, please modify the sentence, *No studies have been performed to evaluate the pharmacokinetics of articaine HCl*
6. Under the Pharmacokinetics – special population – pediatric section, please remove the entire paragraph, and state that the pharmacokinetics of articaine in pediatric population have not been adequately studied.
7. Under Precautions – clinically significant drug interactions, please remove the last sentence:

This sentence actually comes from an assay validation report which indicates no interference in chromatography due to these drugs in the assay for articaine or articainic acid.

/S/ 10/28/98 (draft)

Venkata Ramana S. Uppoor, Ph.
Division of Pharmaceutical Evaluation - II

/S/ 11/9/98 (Final)

RD initialed by John Hunt /S/ 10/28/98

FT initialed by ~~John Hunt~~ /S/ Ph.D. /S/ 11/9/98

CC list: HFD-170: NDA 20,971; Division file; Ken Nolan; HFD-870: Venkata Ramana S. Uppoor, Mei-Ling Chen, John Hunt; HFD-850: Lesko; CDER: Attn: Barbara Murphy

APPENDIX I

STUDY S97001: SINGLE AND MULTIPLE DOSE PK & PD STUDY

A PHASE II STUDY TO EVALUATE SAFETY, EFFICACY AND PHARMACOKINETICS OF A SINGLE DOSE AND MULTIPLE DOSES OF 4% ARTICAINE HYDROCHLORIDE WITH 1:200,000 EPINEPHRINE IN HEALTHY SUBJECTS

Reference: Volumes 18 to 20
Investigator:
Study Location:

Objective: 1. To assess the safety of a single dose (1.7 ml = 68 mg articaine) and multiple doses (5.1 ml = 204 mg articaine) of 4% articaine hydrochloride with 1:200,000 epinephrine
2) To assess the efficacy of a single dose (1.7 ml) of 4% articaine hydrochloride with 1:200,000 epinephrine evaluated by an electric pulp stimulator
3) To obtain pharmacokinetic and metabolism data on articaine hydrochloride with 1:200,000 epinephrine following administration by maxillary infiltration in a single (1.7 ml) and multiple doses (5.1 ml).

Study design:

This study was an open-label, non-randomized, single-center, PK and PD study with single and multiple doses of 4% articaine hydrochloride with 1:200,000 epinephrine administered by maxillary infiltration. The study was conducted in 20 healthy subjects (10 males and 10 females) of age 18 to 50 years with normal, vital incisors without caries or fillings confirmed by X-ray.

Subjects were to fast from 10 hours before to 4 hours after study drug administration. On day 0, for the single dose treatment, subjects were administered 1.7 ml of the study drug by infiltration (into the vestibular fold parallel to the tooth axis at apex level with a needle bevel facing the alveolar bone). On day 1, for the multiple dose treatment, subjects were administered 1.7 ml as described for the single dose above, after close observation for 15 minutes, additional two cartridges (2 x 1.7 ml) were injected by the same infiltration method. A total of 5.1 ml of study drug was administered.

Blood samples for articaine and articainic acid analysis were drawn in each treatment period at 0 (pre-dose), 3, 10, 20, 30, 40, 60 minutes and 1.5, 2, 4, 6, 8, 12 and 24 hours after dosing. Urine samples were collected at 4 hour intervals for 12 hours postdose and then until 24 hours postdose. Since articaine is known to be quickly hydrolyzed in plasma to articainic acid, plasma and urine samples were stabilized by addition of potassium fluoride.

Measurement of pain threshold was done using an electric pulp stimulator, every minute until maximal stimulation was not perceived or the maximal effect was reached and repeated every five minutes thereafter until the maximum stimulation at which pain was sensed decreased by 50%. Onset time, depth and duration of anesthesia are recorded.

PK parameters for articaine and articainic acid were determined by noncompartmental methods. Descriptive statistics of PK and PD parameters are provided.

Results:

ASSAY PERFORMANCE: Assay conducted at [redacted].

ARTICAINE IN PLASMA:
Method used: [redacted]
Range: [redacted] ng/ml
Linearity: Linear within the range, r-squared = [redacted]
QC samples: Low ([redacted] ng/ml), medium ([redacted] ng/ml) and high ([redacted] ng/ml)
Precision: % CV was [redacted] for low QC, [redacted] for medium QC and [redacted] % for high QC levels
Accuracy: The % bias was – [redacted] for low QC, [redacted] for medium QC and [redacted] % for high QC
LOQ = [redacted] ng/ml
Specificity: No interference in peaks of articaine, articainic acid and internal standard, chromatograms acceptable.

ARTICAINIC ACID IN PLASMA:
Method used: [redacted]
Range: [redacted] ng/ml
Linearity: Linear within the range, r-squared = [redacted]
QC samples: Low ([redacted] ng/ml), medium ([redacted] ng/ml) and high ([redacted] ng/ml)
Precision: % CV was [redacted] for low QC, [redacted] for medium QC and [redacted] % for high QC levels
Accuracy: The % bias was – [redacted] for low QC, - [redacted] for medium QC and [redacted] % for high QC levels
LOQ = [redacted] ng/ml
Specificity: No interference in peaks of articaine, articainic acid and internal standard, chromatograms acceptable.

ARTICAINE IN URINE:
Method used: [redacted]
Range: [redacted] ng/ml
Linearity: Linear within the range, r-squared = [redacted]
QC samples: Low ([redacted] ng/ml), medium ([redacted] ng/ml) and high ([redacted] ng/ml)
Precision: % CV was [redacted] for low QC, [redacted] for medium QC and [redacted] % for high QC levels
Accuracy: The % bias was – [redacted] for low QC, [redacted] for medium QC and [redacted] % for high QC
LOQ = [redacted] ng/ml
Specificity: No interference in peaks of articaine, articainic acid and internal standard, chromatograms acceptable.

ARTICAINIC ACID IN URINE:
Method used: [redacted]

Range: —— ng/ml
Linearity: Linear within the range, r-squared = ——
QC samples: Low (— ng/ml), medium (—ng/ml) and high (— ng/ml)
Precision: % CV was — for low QC, — for medium QC and — % for high QC levels
Accuracy: The % bias was - — for low QC, — for medium QC and — % for high QC levels
LOQ = — ng/ml
Specificity: No interference in peaks of articaine, articainic acid and internal standard, chromatograms acceptable.

The sponsor has also evaluated the assay performance to obtain total articaine & articainic acid in urine after hydrolysis of the conjugates. Further, the validation report also provided satisfactory —— stability —cycles) and stability for — days at - —°C after addition of sodium fluoride.

Assays were found to be acceptable.

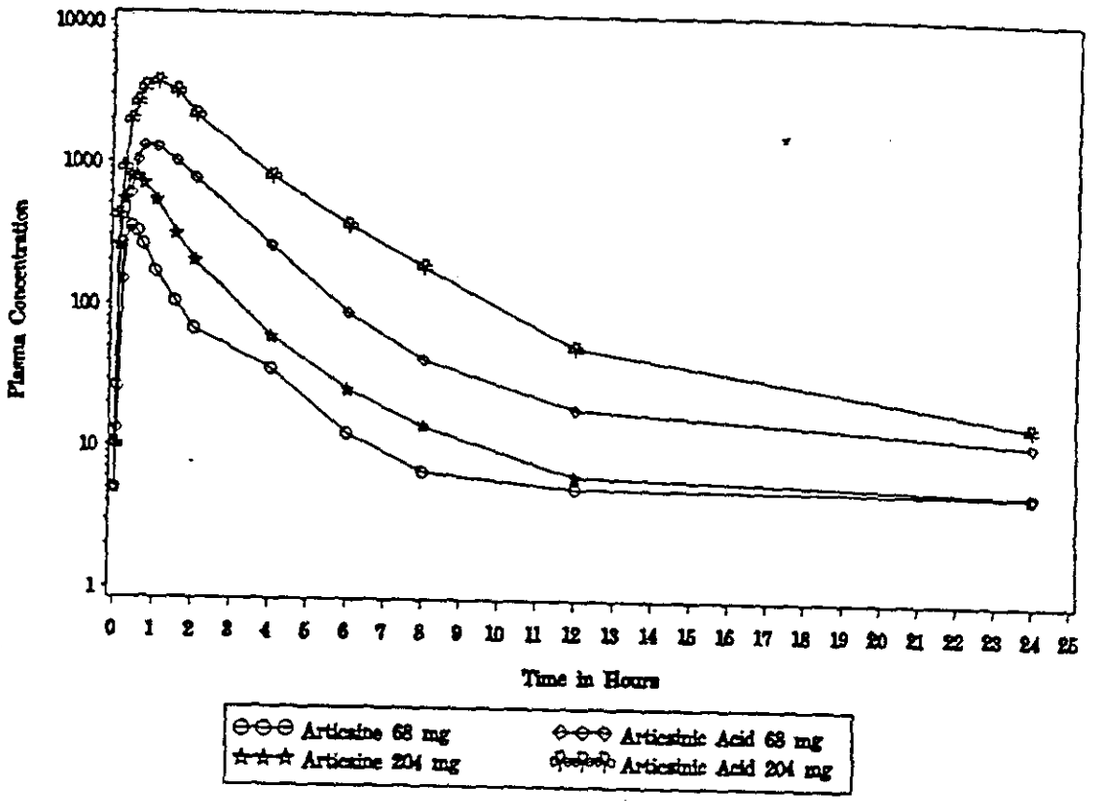
EFFICACY:

Following a single dose injection of 1.7 ml of 4% articaine hydrochloride with 1:200,000 epinephrine, the mean time to onset of anesthesia (time to lack of perception at maximum stimulation with a pulp stimulator) was 3.65 ± 0.39 minutes. The mean duration of anesthesia (time from onset of anesthesia to decrease from maximum stimulation by 50%) was 68.20 ± 8.3 minutes.

Mean (and standard deviation) pharmacokinetic parameters for articaine and articainic acid are shown in the following table.

PK parameters	Articaine 68 mg	Articaine 204 mg	Articaine 68 mg	Articaine 204 mg
	Articaine PK		Articainic acid PK	
Cmax, ng/ml	384.8 (164.6)	899.4 (363.3)	1429.2 (513.5)	3793.1 (795.5)
Tmax, hr	0.4 (0.1)	0.8 (0.2)	0.9 (0.3)	1.3 (0.2)
T1/2, hr	1.8	1.6	1.4	1.7
AUC0-inf, ng.hr/ml	631.3 (134.6)	1541.7 (354.4)	3751.1 (885.2)	11543.1 (2340.9)
Vd, L/kg	4.2 (1.4)	4.7 (1.5)	0.54	0.65
Cl, ml/min	1879.4 (431.1)	2322.7 (561.2)	316	309
Clr, ml/min	36.3 (11.8)	50.2 (23.4)	175.6 (44.6)	160.6 (41.7)
Urine excretion 0-4 hr, mg	1.08 (0.54)	3.47 (1.61)	29.90 (8.32)	77.13 (16.83)
Urine excretion 4-8 hr, mg	0.22 (0.10)	0.66 (0.28)	5.98 (2.73)	20.57 (8.66)
Urine excretion 8-12 hr, mg	0.05 (0.03)	0.16 (0.06)	1.04 (0.66)	4.27 (1.71)
Urine excretion 12-24 hr, mg	0.02 (0.01)	0.07 (0.05)	0.24 (0.14)	1.33 (1.13)

Mean plasma concentration-time curves for articaine and articainic acid following the 2 doses are shown in the following figure.



Articaine was rapidly absorbed after single 68 mg dose administration with a Tmax of about 0.4 hours. The elimination half-life was about 1.8 hours. The plasma concentration time profiles of articaine and articainic acid followed either a one or two compartment model.

Due to analytical difficulties, the articainic acid glucuronide could not be measured. However, it is estimated that about 10% articainic acid is excreted as glucuronide. Based on the urinary excretion of articaine and articainic acid, at least 50% of the administered dose is excreted as articainic acid. This supports the literature data that the major metabolite of articaine is articainic acid.

Conclusions: Following the two doses of articaine, 68 and 204 mg administered by maxillary infiltration injection, approximate dose proportionality in pharmacokinetics of articaine and articainic acid were observed. Peak plasma concentrations of articainic acid were 4 to 7 fold higher than articaine. Articaine is rapidly metabolized to articainic acid.

Comments:

1) This study had only two doses, therefore, only approximate dose proportionality in PK could be obtained.
2) Epinephrine concentrations have not been measured in this study, however, considering the low doses used, only low epinephrine concentrations are likely to occur.
3) This study showed that articainic acid is the primary metabolite of articaine. However, this study was not designed to obtain mass balance information.

GENDER EFFECT

The mean (& standard deviation) PK parameters classified by gender are shown in the following table:

Articaine 68 mg dose			Articaine 204 mg dose		
PK parameters	Males	Females	PK parameters	Males	Females
Articaine PK:			**Articaine PK:**		
Cmax, ng/ml	405.5 (177.93)	364.0 (156.76)	Cmax, ng/ml	900.0 (409.00)	898.7 (333.69)
Tmax, hr	0.40 (0.17)	0.43 (0.08)	Tmax, hr	0.82 (0.23)	0.80 (0.21)
T1/2, hr	1.76	1.76	T1/2, hr	1.57	1.57
AUC0-inf, ng.hr/ml	634.55 (139.40)	627.95 (137.09)	AUC0-inf, ng.hr/ml	1526.34 (398.68)	1557.09 (325.20)
Vd, L/kg	4.03 (1.51)	4.45 (1.38)	Vd, L/kg	4.08 (1.47)	5.26 (1.38)
Cl, ml/min	1864.73 (417.29)	1893.96 (466.53)	Cl, ml/min	2376.20 (667.24)	2269.13 (461.84)
Clr, ml/min	**28.30 (8.12)**	**45.18 (8.44)**	Clr, ml/min	46.17 (24.73)	55.34 (22.05)
Clcreat, ml/min	130.41 (18.16)	120.13 (24.43)	Clcreat, ml/min	130.41 (18.16)	120.13 (24.43)
Articainic acid PK:			**Articainic acid PK:**		
Cmax, ng/ml	1218.1 (353.89)	1640.2 (576.5)	Cmax, ng/ml	3494.8 (834.96)	4091.3 (664.27)
Tmax, hr	0.95 (0.29)	1.0 (0.25)	Tmax, hr	1.32 (0.20)	1.3 (0.20)
T1/2, hr	1.40	1.40	T1/2, hr	1.72	1.72
AUC0-inf, ng.hr/ml	3484.33 (790.08)	4017.95 (933.64)	AUC0-inf, ng.hr/ml	10701.99 (2169.9)	12384.2 (2299.5)
Clr, ml/min	191.60 (51.76)	159.61 (30.86)	Clr, ml/min	175.49 (50.90)	145.74 (24.21)

CONCLUSION: The only gender effect was the statistically significant difference in renal clearance of articaine after administration of 68 mg articaine as single dose. According to the sponsor, after single dose administration of 68 mg articaine, the renal clearance in females of 45 ml/min and in males of 28 ml/min was statistically significant at $p<0.01$. However, there were no significant differences in plasma PK of articaine or articainic acid, as well as the renal clearance after multiple dose.

COMMENTS: Since articaine is a local anesthetic, the systemic levels can affect the safety but not efficacy to a large extent. Further, articaine is rapidly metabolized to articainic acid in vivo. Only a small amount of articaine is excreted unchanged in urine. Since the renal clearance after single dose is the only parameter that showed gender differences, this may not be clinically relevant. Hence, unless clinically significant gender differences are observed in clinical trials, no dosage adjustment is necessary. However, the medical officer for this application is requested to look for gender differences in safety of articaine.

PROTEIN BINDING, IN VITRO METABOLISM AND STABILITY OF ARTICAINE IN HUMAN SERUM:

PROTOCOL 10337/97 – METABOLISM OF ARTICAINE BY HUMAN ISOENZYMES, PROTEIN BINDING AND STABILITY OF ARTICAINE IN HUMAN SERUM IN VITRO INCLUDING VALIDATION OF THE ANALYTICAL METHOD

Volume: 21
Study site:
Objective:

To determine the metabolism of articaine by human isoenzymes, protein binding and stability of articaine in human serum in vitro including validation of the analytical method.

Study Design:

IN VITRO METABOLISM BY CELL MICROSOMES CONTAINING HUMAN P450:

Identification of CYP isoforms that metabolize cilostazol: A reaction mixture containing about 250 µg/ml protein (human lymphoblastoid cell microsomes) containing different human CYP450 isoenzymes, 1000 and 4000 ng/ml articaine and NADP were incubated at 37°C for 3 hours. The supernatant samples were then analyzed for articaine and articainic acid using —— The concentrations of articaine studied are in the range of concentrations achievable in regular use of this product.

Results: % of articaine metabolized by cytochrome P450 isoenzymes along with the % of articaine recovered as articainic acid is shown in the table below:

Enzyme	Articaine metabolized (pmole)	% articaine metabolized	Articainic acid found (pmole)	% articaine recovered as articainic acid
Low articaine concentration (1000 ng/ml or 3516 pmole)				
Control	21	0.6	-	-
CYP3A4	274	7.8	246	89.8
CYP2E1	186	5.3	108	57.7
CYP2D6-val	542	15.4	465	85.9
CYP2C8	426	12.1	417	97.9
CYP2C19	264	7.5	248	93.9
CYP2B6	429	12.2	305	71.0
CYP2C9-arg	288	8.2	253	87.7
CYP2A6	454	12.9	361	79.7
CYP1A2	345	9.8	351	102.0
CYP1A1*	35	1.0	0	-
CYP1A1**	1656	-	-	-

High articaine concentration (4000 ng/ml or 14065 pmole)				
Control	0	0.0	-	-
CYP3A4	651	4.6	748	115.0
CYP2E1	464	3.3	774	166.7
CYP2D6-val	1382	9.8	1429	103.4
CYP2C8	1129	8.0	1210	107.2
CYP2C19	823	5.9	735	89.3
CYP2B6	731	5.2	724	98.9
CYP2C9-arg	738	5.2	616	83.4
CYP2A6	1164	8.3	1162	99.8
CYP1A2	921	6.5	896	97.3
CYP1A1*	0	0.0	0	-
CYP1A1**	5556	-	-	-

* Protein concentration 42.5 μg/ml

** Protein concentration 255 μg/ml

Conclusion: Results from this study indicate that almost all the CYP isoenzymes metabolize articaine but only to a minor extent (about 10%). Results also indicate almost quantitative recovery of the metabolized articaine as articainic acid. Data suggests some saturation of metabolism since the % metabolized at higher concentration of articaine is less than at the lower concentrations. Since the extent of metabolism by individual isoenzymes is relatively low, this may not be a major pathway of articaine metabolism.

Comments: While, based on this data, it appears that cytochrome P450 enzymes play a minor role in metabolism of articaine to articainic acid, it would have been beneficial to conduct this study in human liver microsomes (in addition to individual isoenzymes) to get an estimate of the extent of metabolism due to the CYP isozymes as a whole.

PROTEIN BINDING OF ARTICAINE:

Protein binding of articaine to human serum albumin (HSA), human γ-globulin (HGG) and a fraction of human α- and β-globulins (HABG) was determined by [redacted] method [redacted] conducted at 37°C. Articaine was studied at concentrations of 500 and 2000 ng/ml and HSA at 40 mg/ml, HGG at 15 mg/ml and HABG at 20 mg/ml in phosphate buffered saline at pH of 7.4. The protein concentrations were chosen with regard to normal human serum protein concentrations. Articaine concentrations tested are within the range of plasma concentrations achievable.

Results:

% binding of articaine to various proteins are shown below:

Protein	Articaine conc.	6 hr at 37 deg C	24 hr at 37 deg C
Albumin	488 ng/ml	68.6%	80.1%
	1753 ng/ml	68.4%	81.5%
γ-globulin	488 ng/ml	8.5%	28.0%
	1753 ng/ml	8.6%	19.4%
α/β-globulin	488 ng/ml	62.6%	72.7%
	1753 ng/ml	62.5%	74.9%

Conclusion: % protein binding to albumin and α/β-globulin is independent of articaine concentration but depends on the protein. Binding to γ-globulin appears to be saturable.

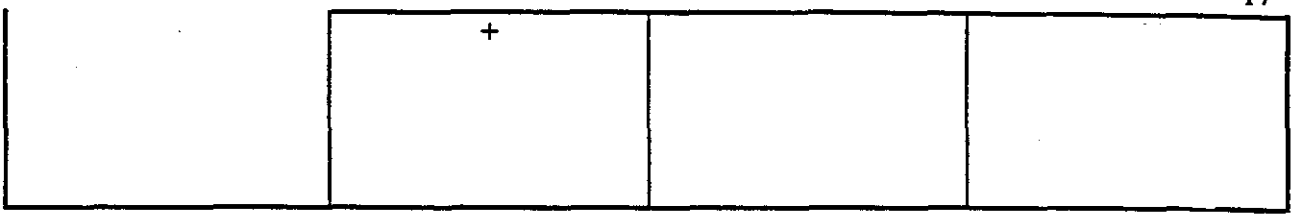
Comment: Protein binding has been determined with individual selected proteins. The protein binding in plasma for both articaine and articainic acid has not been determined.

EX VIVO STABILITY IN HUMAN SERUM:

The stability of articaine in pooled human serum was investigated at two concentrations for — hours and — days at room temperature and at — °C. Additionally, the influence of an esterase inhibitor (sodium fluoride) on the articaine stability was determined.

STABILITY OF ARTICAINE IN HUMAN SERUM (*EX VIVO*)

Articaine conc	NaF 200 µl of 1% soln./ml serum	Storage conditions	% articaine remaining
100 ng/ml	-		
	+		
2000 ng/ml	-		



CONCLUSION: When samples containing articaine were stored at —degrees C after stabilization with sodium fluoride, articaine was stable for at least one week.

WAIVER FOR SEPTANEST — (containing 4% articaine along with 1:100,000 epinephrine)

The formulation Septanest — containing 4% articaine along with 1:200,000 epinephrine was the formulation tested in the pharmacokinetic study to characterize the PK of articaine. Waiver for bioavailability of Septanest — can be granted since the two formulations are proportionally similar with respect to articaine. The only difference is in epinephrine. The primary focus of the PK of this NDA is on articaine and its metabolite. It has been previously agreed with the agency that as long as the sponsor obtains PK data on articaine and its metabolite to support literature data available, this is satisfactory, since articaine has been used in several countries for multiple number of years.

SUMMARY OF LITERATURE REFERENCES:

a) Clinical pharmacokinetics of articaine after oral and intramuscular administration, Kirch W. et al, Schweiz. Mschr. Zahnheilk, 1983, 93(9), 714 – 719: This study used a different formulation Ultracaine DS which showed that the elimination half life of articaine after oral (submucosal injection) was 25.3 minutes while that after I.M. administration was 39.8 minutes.

b) Pharmacokinetics of articaine during mandibular nerve block, Muller et al, Regional Anaesthesie, 1991, 14: 52 – 55: It is not clear what formulation was used for mandibular nerve block, however, it is known that it contains 4% articaine with 1:200,000 epinephrine. A half-life of 20 minutes was reported for articaine.

c) Pharmacokinetic study carried out using radiolabeled ^{35}S Carticaine, Hoffer et al: The half life of radioactivity was as high as 31.5 hours after I.M. administrations. After I.V. administration, the terminal half-life was as long as 69.7 hours. About 90% of the dose was excreted in urine and about 1.5% in feces.

d) Clinical effects and pharmacokinetics of articainic acid in one volunteer after intravenous administration, Van Oss et al, Pharm. Weekbl (Sci) 1988: 10: 281-6: Articainic acid did not show any local anesthetic activity. Based on previous data, it was suggested that after epidural administration of articaine, the drug is metabolized into articainic acid (40 to 80% is excreted in urine as articainic acid) and its glucuronide (15%). The short half life of articainic acid is confirmed and found to be 64 minutes. Protein binding of articainic acid is

89.3%.

e) Serum levels of articaine 2% and 4% in children, Jakobs et al, Anesth Prog 42: 113-115, 1995: This is a PK study of articaine conducted in 27 children 3 to 7 years of age, who underwent dental procedures under intubation anesthesia. Patient group 1 (n = 14) received 2 mg/kg of 2% articaine solution with epinephrine 1:200,000 (Ultracain 2%). Group 2 (n = 13) received 2 mg/kg of 4% articaine with epinephrine 1:200,000 (Ultracain DS) as infiltration anesthesia in the vestibule of the upper or lower jaw. Blood samples were obtained at 0, 2, 5, 10 and 20 minutes after local anesthesia. The results are as follows: Cmax with 2% articaine is 1060 $\pm$ 405 ng/ml, in the 4% articaine group, the Cmax is 1382 $\pm$ 328 ng/ml; tmax with 2% articaine is 7.44 min and with 4% articaine is 7.78 minutes; half life with 2% articaine is 18.5 minutes and that of the 4% articaine is 23.6 minutes; plasma clearance with 2% articaine is 105.6 ml/min and with 4% articaine is 25.02 ml/min. The authors compared this to the PK in adults obtained in the paper by Kirsch et al and stated that the concentrations achieved in adults and children are comparable. However, some of the drawbacks of this study are as follows:

- Details of the Ultracain and Ultracain DS formulation are unknown. Therefore, one cannot compare this to Septanest product of articaine which is the subject of this NDA.
- It is unclear how the authors could estimate elimination half life (of about 20 minutes) when samples were only drawn for 20 minutes after dosing.
- Further no estimate of exposure (AUC) has been obtained.

CONCLUSION: Due to these drawbacks, one should not allow any pediatric claims for the Septanest package insert based on this literature report.