CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-451

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-451	Submission Date(s): 1/22/02
Brand Name	Oraqix™ Periodontal Gel
Generic Name	Lidocaine 2.5% and prilocaine 2.5% Gel
Primary Reviewer	David Lee
Secondary Reviewer	Suresh Doddapaneni
OCPB Division	DPE 2
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor	DENTSPLY Pharmaceutical
Related NDA(s)	19-941 EMLA® Cream – 2.5%/2.5 % lidocaine / prilocaine
	20-962 EMLA® Disc - 2.5%/2.5 % lidocaine / prilocaine
Relevant IND(s)	52,677
Submission Type; Code	505(b)(1); 1 S
Formulation; Strength(s)	Lidocaine 2.5% (25 mg/g) and prilocaine 2.5% (25 mg/g) Gel
Proposed Indication	For localized anesthesia in periodontal pockets for scaling and/or root planing
Proposed Dosage Regimen	Recommended dose is, on average, 1 cartridge (1.7 g gel containing 42.5 mg lidocaine base and 42.5 mg prilocaine base) or less of Oraqix™ for one quadrant of the dentition. The maximum recommended dose of Oraqix™ at one treatment session is 5 cartridges (8.5 g gel containing 212.5 mg lidocaine base and 212.5 mg prilocaine base).

1 Executive Summary

DENTSPLY Pharmaceutical, has submitted a New Drug Application, NDA 21-451 seeking approval for Oraqix™ Periodontal Gel (lidocaine / prilocaine gel, 2.5 % / 2.5%), for localized anesthesia in periodontal pockets for scaling and/or root planing (SRP).

The Applicant stated that Gel is a pharmaceutical extension in the development program for EMLA® (eutectic mixture of lidocaine and prilocaine) Cream. The 5% Gel consists of the active ingredients lidocaine and prilocaine in the same concentrations as in EMLA® Cream 5%.

The Applicant's rationale for developing the Gel are as follows:

1. At present, the main anesthetic techniques used for SRP are either nerve block or infiltration alone or a combination of the two methods
2. Topical anesthetics are occasionally used
3. The main drawbacks with injections are distress associated with needle insertion and inconvenient anesthesia of the surrounding soft tissue
4. Topical anesthetics available today have a low efficacy

5. A non-injectable anesthetic therapy with high efficacy and short duration is warranted to avoid the distress of needles and to make the treatment comfortable without inconvenient numbness.

It should be noted that EMLA® 5% Cream (N 19-941) was approved by the Agency in 1992 as a topical anesthetic for use on normal intact skin for local analgesia in adults, children, and infants less than 1 month old. In 2000, an additional indication (use on genital mucous membranes for superficial minor surgery and as a pretreatment for infiltration anesthesia) was awarded to EMLA® Cream. It is also noted that EMLA® 5% Anesthetic Disc, a single-dose topical adhesive system, was approved for the similar indication in 1998 (N 20-962).

The Applicant stated that they have not licensed the proposed Gel to any other sponsor and the product is not marketed nor has an application been filed for its marketing outside the United States. In United States, the clinical trials essential to this NDA were conducted under IND 52,677. The Applicant submitted a total of 3 pharmacokinetic/biopharmaceutic studies (A1, A2, and A3) under Section 6 of the NDA submission. Additionally, the Applicant submitted supporting literature information on lidocaine, prilocaine, and its' metabolites. The overall theme of clinical trials were that the Gel was applied, in order to maximize the rate of absorption for the local effect, as rapidly as possible (within 6-9 minutes) and remained within the pockets for as long as possible (i.e., during the time of probing and SRP) in all periodontal pockets.

With respect to pediatric studies, the Applicant submitted a request for deferral of pediatric studies for all pediatric patients. The Applicant stated that necessary studies are impossible or highly impractical due to the fact that the number of pediatric patients suffering from periodontitis is too small or too geographically dispersed to make such studies possible.

Exposure-response (E-R) relationship

The submitted information suggests that there are no apparent exposure – efficacy response relationships, between the primary and secondary efficacy endpoints (visual analogue scale (VAS) and verbal rating scale (VRS), respectively) and plasma concentrations of active ingredients, lidocaine and prilocaine.

However, it is well known that there are toxic effects due to lidocaine and prilocaine. Therefore it is pertinent to look into the systemic exposure of lidocaine and prilocaine and its' metabolites. It is well documented that the acute CNS and cardiovascular toxicity of local anesthetics is related to their plasma concentrations. Due to similar mechanism of action, the toxicity of lidocaine and prilocaine is thought to be additive in this Gel.

It is documented that pharmacological and CNS toxic effects of lidocaine occur at plasma concentrations as low as 1 and 5 -6 µg/mL, respectively; some of the toxic effects observed at lidocaine plasma concentrations of 5 – 10 µg/mL include muscular irritability, convulsions, and coma. Prilocaine's CNS toxic effects are expected to be similar to that of lidocaine. Therefore, the combined target plasma lidocaine/prilocaine concentrations should be approximately 1 µg/mL for systemic exposure/toxicity.

One (Study A3) of the pharmacokinetic studies evaluated plasma concentrations of lidocaine, prilocaine, 2,6-xylidine, *o*-toluidine, and methemoglobin (metHB) following administration of the highest recommended dose of Oraqix Periodontal Gel 8.0 – 8.7 g. The data revealed that all values were below toxic levels; the plasma concentrations of lidocaine and prilocaine were below toxic levels. Since the metabolites of o-toluidine are known to potentially induce formation of methemoglobin (metHB; metHB is formed when Fe^{+2} is oxidized to Fe^{+3}. In the body, the circulating metHB levels usually remain < 1% of hemoglobin (Hb) levels since NADH reductase reduces Fe^{+3} back to Fe^{+2}.), the metHB values were assessed as well. All subjects had normal values of below 2%. At least 10% metHb is needed in order to induce clinical signs of

methemoglobinemia. o-Toluidine is a weak genotoxin under in vitro conditions and a weak carcinogen in animals.

Lidocaine, prilocaine, 2,6-xylidine, o-toluidine systemic concentrations

After single application of 0.1 - 0.7 g of Dental Gel 5 % (Study A1), the highest individual plasma levels were 26.7 ng/ml for lidocaine and 9.9 ng/ml for prilocaine at 37-64 minutes post application. This study did not measure any metabolite concentrations.

After single application of 0.9 – 3.5 g of Dental Gel 5% (Study A2), the highest observed individual plasma concentrations of lidocaine and prilocaine were 266 ng/ml and 118 ng/ml, respectively. The highest observed plasma concentrations of 2,6-xylidine and o-toluidine values were 14.2 ng/mL and 16 ng/mL, respectively.

After single application of 8 – 8.7 g of Dental Gel 5% (Study A3), the highest observed individual plasma concentrations of lidocaine and prilocaine were 552 and 181 ng/mL, respectively. The highest observed plasma concentrations of 2,6-xylidine and o-toluidine values were 32 ng/mL and 44 ng/mL, respectively.

Food effect

Food effect studies were not conducted.

Drug interaction

Drug interaction studies were not conducted.

Gender differences

Gender studies were not conducted.

Pediatric population

The Applicant has requested a deferral to study the product in pediatric population.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-451 (Oraqix™ Periodontal Gel) submitted on Jan 22, 2002. The information contained in the NDA is acceptable; however, the recommended Labeling comments by the Agency should be forwarded to the Applicant.

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3 Summary of CPB Findings

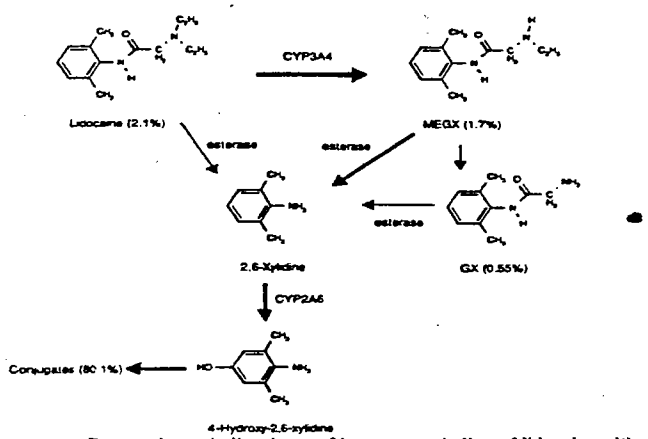
Background information on Lidocaine and prilocaine from the NDA

Prilocaine and lidocaine bases are both slightly soluble in water and very soluble in ethanol and acetone at 20°C. The dissociation constants (pKa) of lidocaine and prilocaine are 7.86 and 7.89, respectively. Hence, at a pH above the pKa, more than 50% of the active components will be present in the uncharged, hydrophobic form, whereas more than 50% will be present in the charged, hydrophilic form at a pH below the pKa. At the chosen pH of the formulation, approximately 50% of lidocaine and prilocaine are present in ionized form and 50% in unionized form.

It is documented that lidocaine and prilocaine exhibit a bi-phasic dose-dependent vascular response. At low concentrations, they cause vasoconstriction, and at higher concentrations, they cause vasodilatation.

Some basic pharmacokinetic (PK) parameters in adults are available for lidocaine and prilocaine. Post intravenous (IV) dosing, for lidocaine and prilocaine, the systemic clearance (CL), volume of

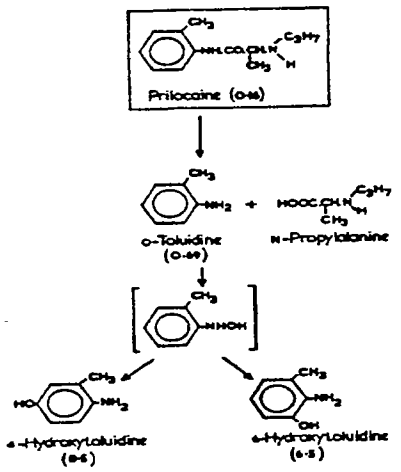
distribution (Vd), and terminal half-life ($T_{1/2}$) and in vitro plasma protein binding (%) were 13 ml/min/kg, 1.5 l/kg, 1.8 hr, and 70% (mainly to α_1-acid glycoprotein), respectively, and 38 ml/min/kg, 2.6 l/kg, 1.2 hr, and 55%, respectively.



Proposed metabolic scheme of human metabolites of lidocaine with percentage of dose recovered after intravenous administration. Bold arrows indicate major routes.

The main metabolites formed from lidocaine are monoethylglycine xylidide (MEGX), glycinexylidide (GX), 2,6-xylidine and 4-hydroxy-2,6-xylidine. The N-dealkylation to MEGX is considered to be mediated by both CYP1A2 and CYP3A4, but CYP3A4 seems to be the most important. The metabolite 2,6-xylidine is converted to 4-hydroxy-2,6-xylidine by CYP2A6 [AstraZeneca data from EMLA Cream] and the latter is the major urinary metabolite in man.

MEGX has an anti-arrhythmic and convulsant activity similar to that of lidocaine and a somewhat longer half-life. It is considered to contribute to the anti-arrhythmic effects and toxicity during lidocaine infusion. GX has a weak anti-arrhythmic effect but lacks convulsant activity and has a half-life of approx. 10 hours.



Pathways for the human biotransformation of prilocaine

Prilocaine is split at the amide linkage to o-toluidine, which is converted further to 4- and 6-hydroxytoluidine. After a subcutaneous dose of 20 mg/kg prilocaine to volunteers, a mean of

34% of the dose was recovered in 24-h urine as 6-hydroxytoluidine, 2.7% as 4-hydroxytoluidine and 0.75% as o-toluidine. After 7.4 hours post injection (min-max 6-11 h), half the excreted amounts of the hydroxylated metabolites was in urine. The excretion of o-toluidine was more rapid, half the amount being excreted at about 3 hours after a prilocaine injection. Thus, the 24-h urine probably reflects the total amount of toluidine metabolites excreted. The dose is generally expressed as prilocaine HCl. If prilocaine is completely transformed to o-toluidine, 100 mg prilocaine HC1 is converted to 42 mg o-toluidine, i.e. 42% of the dose. Consequently, the total excretion of 37% of the dose as toluidine or its hydroxylated metabolites in the above study indicates an essentially complete conversion of prilocaine to o-toluidine in man.

EMLA® Cream

For comparison, the Applicant stated that the absorption of lidocaine and prilocaine from EMLA® Cream into the systemic circulation has been documented for intact skin and genital and gingival mucosa. Following application of 10 g EMLA® cream to the face for 2 hours, mean maximum levels of lidocaine and prilocaine, 150 ng/mL and 58 ng/mL respectively, were reached after 1.5-3 hours. Peak plasma concentrations of lidocaine and prilocaine following application of 10 g EMLA® cream for 10 minutes to genital mucosa, 180 ng/mL and 150 ng/mL, were reached after 20-45 minutes. The application of 4 g EMLA® cream for 4 minutes to the gingival mucosa in 25 patients resulted in maximum individual Cmax values of 470 ng/mL (5 minutes after application) and 210 ng/mL (10 minutes after application) for lidocaine and prilocaine respectively. Initial symptoms of pharmacological and CNS toxicity would be expected to occur at 1000 and 5000-6000 ng/ml, respectively.

Oraqix Periodontal Gel

1. After single application of 0.1 - 0.7 g of Dental Gel 5 %, in the 2 and 5-min groups, the mean (±SD) lidocaine and prilocaine plasma concentrations were 10.4 (±5.9) and 12.5 (±8.5) ng/ml and 4.2 (±2.9) and 3.3 (±1.7) ng/ml, respectively. The time point was at 37-64 minutes post application (a single plasma sample was obtained at 37 – 64 min. post Gel application). In the 2 and 5-min groups, the highest individual plasma concentrations of lidocaine and prilocaine were 21.8 and 26.7 ng/ml and 9.9 and 7.0 ng/ml, respectively. No metabolite concentrations were determined in this study.

2. After single application of 0.9 to 3.5 g Dental Gel 5%, corresponding to 0.05-0.13 g Dental Gel 5% per tooth, the mean (±SD) lidocaine Cmax was 181.7 (±52.7) ng/mL and ranged between 99 and 266 ng/mL. The tmax was reached between 20 and 40 min post Gel application with a mean (±SD) of 31 (±5.7) min. The mean AUCt for lidocaine was 10,220 ± 3,127 ng.min/mL. The mean (±SD) prilocaine Cmax was 76.7 (±27.2) ng/mL and ranged between 39 and 118 ng/mL. The tmax was reached 20 to 40 min after the start of application of Periodontal Gel with a mean (±SD) of 30 (±4.7) min. The mean AUCt for prilocaine was 3,846 ± 1,032 ng.min/mL. The highest observed individual plasma concentrations of lidocaine and prilocaine were 266 ng/ml and 118 ng/ml, respectively. Individual 2,6-xylidine and o-toluidine Cmax values were ranged from 13-117 (highest value of 14.2 ng/mL) nmol/L and 48-146 (highest value of 16 ng/mL) nmol/L, respectively, and, occurred 60-75 and 60-90 minutes after application.

3. After single application of 8 – 8.7 g Dental Gel 5 %, the mean (±SD) lidocaine Cmax was 284 (±122) ng/mL and ranged between 157 and 552 ng/mL. The tmax was reached 40 min. post Gel application with a median of 200 (range of 120 - 220) min. The mean AUCt was 72,773 ng.min/mL. The mean (±SD) prilocaine Cmax was 106 (±45) ng/mL and ranged between 53 and 181 ng/mL with a median (min-max) tmax of 200 (120 - 200) min. The highest individual Cmax was seen 200 min after the start of application of the gel. The mean AUCt was 24,456 ng.min/mL. The highest observed individual plasma concentrations of lidocaine and prilocaine were 552 and 181 ng/mL, respectively. The mean (±SD) terminal half-life was 3.6

(±1.33) hours for lidocaine and ranged between 2.17 and 6.48 hours. The mean (±SD) half-life for prilocaine was 2.82 (±1.0) hours and ranged between 1.97 to 5.72 hours. The mean (±SD) 2,6-xylidine Cmax was 18 (±8.4) ng/mL and ranged between 8 and 32 ng/mL. The tmax was reached 175-240 min post Gel application with a median of 239 min (range of 175 – 240) min. The mean AUCt was 5380.13 ng.min/mL. The mean terminal half-life was 475 min. (±242.8) and ranged between 226 and 1069 min. The mean (±SD) o-toluidine Cmax was 25 ng/mL and ranged between 13 and 44 ng/mL. The tmax was reached 90-240 min after the start of application. The mean AUCt was 7319.6 ng.min/mL. The mean terminal half-life was 241 (±67.5) min. and ranged between 121 - 338 min.

4. The scatter plots of lidocaine and prilocaine Cmax vs. dose indicate a dose proportional increase between Cmax and dose administered. In the model used, the regression slope for ln(Cmax) vs. ln(dose) was statistically significantly different from zero for prilocaine (p=0.02), but not for lidocaine (p=0.0503). In the linear regression, about 53% of the variance in Cmax for prilocaine could be explained by the dose given. The corresponding value was 40% for lidocaine. Using this model, Cmax-values for prilocaine and lidocaine are estimated to increase by factors of 1.6 and 1.4 respectively when the dose of Dental Gel 5% is doubled.

5. The submitted information suggests that there is no apparent exposure – efficacy response relationships, between the primary and secondary efficacy endpoints (visual analogue scale (VAS) and verbal rating scale (VRS), respectively) and plasma concentrations of active ingredients, lidocaine and prilocaine.

6. No gender studies were conducted.

7. Clinical and to-be-marketed formulations were used in PK studies; no differences between the formulations were observed using chemical compositional and molecular analyses. Therefore, there are no issues related to bioequivalence. To-be-marketed formulation was used in one of the pivotal clinical safety and efficacy trials.

8. Drug-drug interaction studies were not conducted.

9. The Applicant submitted a deferral to study the proposed Gel in pediatric population.

4 QBR

4.1 General Attributes

What is Oraqix?

Oraqix™ Periodontal Gel 5% is a eutectic oil-in-water mixture (thermo-reversible gelling system, which is a low-viscosity fluid at room temperature, 24 - 32°C, and becomes an elastic gel at higher temperature, 37°C and higher) after introduction of 2.5% lidocaine and 2.5% prilocaine. (As a comparison the following dental anesthetics are currently marketed: Hurricaine, a 20% benzocaine gel approved for transient topical anesthesia on all accessible mucous membranes, and a DentiPatch, topically applied patch of lidocaine (approved in 1996 as NDA 20-575) for pre injection-site anesthesia)

What is the composition of Oraqix Gel?

INGREDIENT	QUANTITY	FUNCTION
Lidocaine	25 mg	Active ingredient; local anesthetic
Prilocaine	25 mg	Active ingredient; local anesthetic
Poloxamer 188		
Poloxamer 407		
Hydrochloric acid		
Water Purified		

4.2 General Clinical Pharmacology

Is there any exposure-response relationship information for combination tablet?

The submitted information suggests that there are no apparent E-R relationships between the primary and secondary efficacy endpoints (visual analogue scale (VAS) and verbal rating scale (VRS), respectively) and plasma concentrations of active ingredients, lidocaine and prilocaine.

What are lidocaine, prilocaine, 2,6-xylidine, and o-toluidine concentrations after different Gel application?

Study A1: Gel 0.1 – 0.7 g (2.5 – 17.5 mg of lidocaine and prilocaine base)
* Plasma samples taken at 37 – 64 minutes post Gel application.

In the 2 and 5-min groups, the mean (±SD) lidocaine and prilocaine plasma concentrations were 10.4 (±5.9) and 12.5 (±8.5) ng/ml and 4.2 (±2.9) and 3.3 (±1.7) ng/ml, respectively.

In the 2 and 5-min groups, the highest individual plasma concentrations of lidocaine and prilocaine were 21.8 and 26.7 ng/ml and 9.9 and 7.0 ng/ml, respectively.

No metabolite concentrations were determined in this study.

Study A2 : Gel 0.9 – 3.5 g (22.5 – 87.5 mg of lidocaine and prilocaine base)

The mean (±SD) lidocaine Cmax was 181.7 (±52.7) ng/mL and ranged between 99 and 266 ng/mL. The tmax was reached between 20 and 40 min post Gel application with a mean (±SD) of 31 (±5.7) min. The mean AUCt for lidocaine was 10,220 ± 3,127 ng.min/mL.

The mean (±SD) prilocaine Cmax was 76.7 (±27.2) ng/mL and ranged between 39 and 118 ng/mL. The tmax was reached 20 to 40 min after the start of application of Periodontal Gel with a mean (±SD) of 30 (±4.7) min. The mean AUCt for prilocaine was 3,846 ± 1,032 ng.min/mL.

The highest observed individual plasma concentrations of lidocaine and prilocaine were 266 ng/ml and 118 ng/ml, respectively.

Individual 2,6-xylidine and o-toluidine Cmax values were ranged from 13-117 (highest value of 14.2 ng/mL) nmol/L and 48-146 (highest value of 16 ng/mL) nmol/L, respectively, and, occurred 60-75 and 60-90 minutes after application.

Cmax, $t_{max\ start}$ and $t_{max\ end}$ for lidocaine and prilocaine.

	Lidocaine			Prilocaine		
Pat #	Cmax (ng/ml)	$t_{max\ start}$ (min)	$t_{max\ end}$ (min)	Cmax (ng/ml)	$t_{max\ start}$ (min)	$t_{max\ end}$ (min)
101	157	40	33	84	40	33
102	157	30	23	82	30	23
103	127	30	23	50	30	28
104	99	30	23	46	30	23
105	236	20	13	80	20	13
106	181	30	23	62	30	23
108	156	30	24	39	30	24
109	204	30	21	118	30	21
110	234	30	23	94	30	23
111	266	40	32	112	30	32
x ± sd	181.7 ± 52.7	31 ± 5.68	23.8 ± 5.57	76.7 ± 27.2	30.0 ± 4.71	24.3 ± 5.72
median (range)	169 (99-266)	30 (20-40)	23 (13-33)	81 (39-118)	30 (20-40)	23 (13-33)

$t_{max\ start}$ = tmax from start of administration of Dental Gel 5%
$t_{max\ end}$ = $t_{max\ start}$ - time of administration of Dental Gel 5%

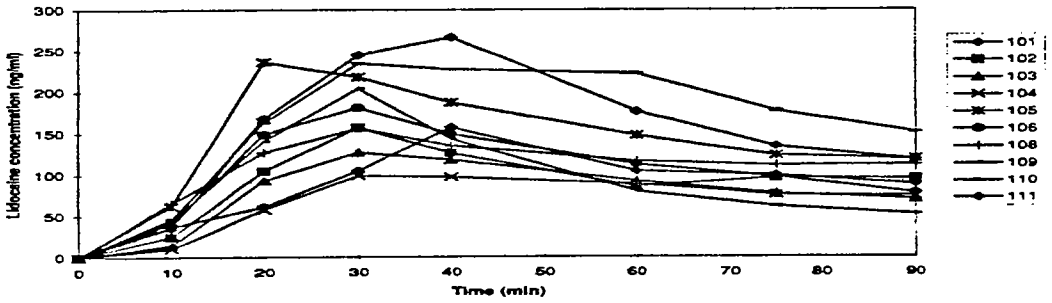
AUCt, AUC∞ and residual (% of AUC∞) for lidocaine and prilocaine.

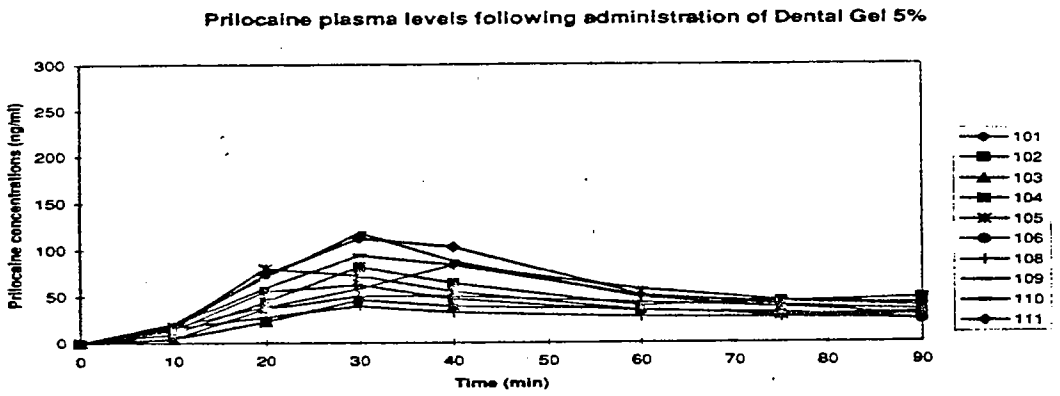
	Lidocaine			Prilocaine		
Pat #	AUCt (ngmin/ml)	AUC∞ (ngmin/ml)	residual (% of AUC∞)	AUCt (ngmin/ml)	AUC∞ (ngmin/ml)	residual (% of AUC∞)
101	8 350	19557	57	4 195	8806	52
102	8 205	144291	94	3 900	-	-
103	7 385	20153	63	3 212	9244	65
104	6 345	89039	93	2 548	-	-
105	13 275	67266	80	3 778	-	-
106	9 938	14940	33	3 235	4280	24
108	10 040	-	-	2 332	6830	66
109	8 722	13609	36	5 012	6798	26
110	15 508	29764	45	4 950	11556	57
111	14 435	28355	49	5 302	8441	37
x ± sd	10 220 ± 3 127	47 442 ± 44 586	61± 23	3 846 ± 1 032	7994 ± 2298	47± 18
median (range)	9330 (6345-15508)	28 355 (13 609-144 291)	57 (33-94)	3 839 (2 332-5 302)	8441 (4280-11556)	52 (24-66)

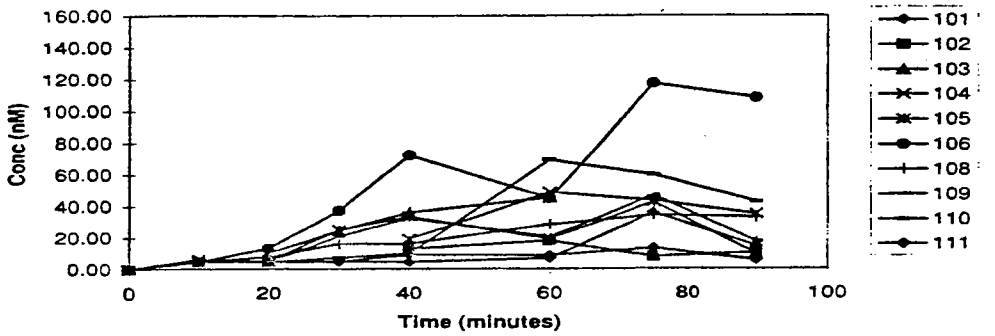
Cmax and t_{max} for lidocaine, 2,6-xylidine, prilocaine and *o*-toluidine

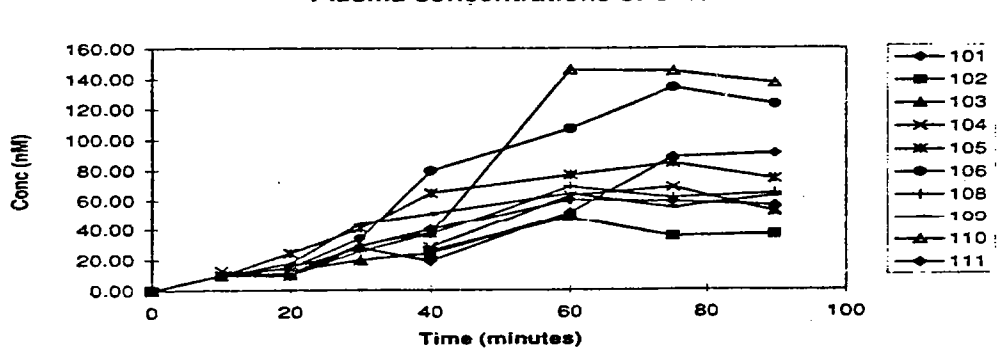
	Cmax (nmol/l) x ± sd (range)	t_{max} (min) median (range)
Lidocaine	777 ± 225 (421-1137)	30 (20-40)
2,6-xylidine	47 ± 29 (13-117)	75 (60-75)
Prilocaine	348 ± 123 (176-536)	30 (30-40)
o-toluidine	82 ± 33 (48-146)	67.5 (60-90)

Lidocaine plasma levels following administration of Dental Gel 5%









Study A3 : Gel 8 – 8.7 g (200.0 – 217.5 mg of lidocaine and prilocaine base)

The mean (±SD) lidocaine Cmax was 284 (±122) ng/mL and ranged between 157 and 552 ng/mL. The tmax was reached 40 min. post Gel application with a median of 200 (range of 120 - 220) min. The mean AUCt was 72,773 ng.min/mL.

The mean (±SD) prilocaine Cmax was 106 (±45) ng/mL and ranged between 53 and 181 ng/mL with a median (min-max) tmax of 200 (120 - 200) min. The highest individual Cmax was seen 200 min after the start of application of the gel. The mean AUCt was 24,456 ng.min/mL.

The highest observed individual plasma concentrations of lidocaine and prilocaine were 552 and 181 ng/mL, respectively.

The mean (±SD) terminal half-life was 3.6 (±1.33) hours for lidocaine and ranged between 2.17 and 6.48 hours. The mean (±SD) half-life for prilocaine was 2.82 (±1.0) hours and ranged between 1.97 to 5.72 hours.

The mean (±SD) 2,6-xylidine Cmax was 18 (±8.4) ng/mL and ranged between 8 and 32 ng/mL. The tmax was reached 175-240 min post Gel application with a median of 239 min (range of 175 – 240) min. The mean AUCt was 5380.13 ng.min/mL. The mean terminal half-life was 475 min. (±242.8) and ranged between 226 and 1069 min.

The mean (±SD) o-toluidine Cmax ranged between 120 and 411 nmol/L (44 ng/mL) and tmax was reached 90-240 min after the start of application. The mean AUCt was 7319.6 ng.min/mL. The mean terminal half-life was 241 (±67.5) min. and ranged between 121 - 338 min.

Cmax and tmax for Lidocaine, prilocaine, 2,6-xylidine, and o-toluidine following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine base, respectively) in periodontal pockets in 11 patients with widespread periodontal disease. Results are presented as mean + SD (min-max). tmax is presented as median (min-max).

	Cmax (ng/mL)	Cmax (nmol/L)	tmax* (min)
Lidocaine	283.8 ± 121.9 (157 – 552)	1211 ± 520 (671-2355)	200 (120-220)
Prilocaine	106.1 ± 44.7 (53 – 181)	482 ± 203 (242-823)	200 (120-200)
2,6-xylidine	18.0 ± 8.4 (8- 32)	148 ± 69 (68 - 260)	239 (175-240)
0-toluidine	25.2 ± 10.9 (13-44)	235 ± 102 (120-411)	220 (90-240)

* from start of application of Dental Gel 5%

(Data source: Appendix 16.2.5. Tables 2.3.1., 2.3.3., 2.3.5., 2.3.7., 2.6.1., 2.6.3., 2.6.5., 2.6.7.)

Pharmacokinetic parameters for lidocaine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	257.00	5.00	0.92	41445.00	49603.00	16.45
102	132.00	5.00	0.99	71688.00	74932.00	4.33
103	263.00	6.00	0.89	119775.00	151291.00	20.83
105	154.00	5.00	0.97	101480.00	109539.00	7.36
201	130.00	5.00	0.99	48461.00	50750.00	4.51
202	222.00	5.00	0.90	50658.00	57941.00	12.57
203	272.00	5.00	0.94	55227.00	64546.00	14.44
204	389.00	5.00	0.91	43103.00	57862.00	25.51
205	140.00	5.00	0.98	50627.00	52680.00	3.90
206	181.00	5.00	0.96	152190.00	171288.00	11.15
207	256.00	5.00	0.75	65858.00	78788.00	16.41
Mean	217.82	5.09	0.93	72773.82	83565.45	12.50
SD	79.91	0.30	0.07	36234.71	42328.73	7.11
Min	130.00	5.00	0.75	41445.00	49603.00	3.90
Max	389.00	6.00	0.99	152190.00	171288.00	25.51

(Data source: Appendix 16.2.5. Table 2.12.1.)

Pharmacokinetic parameters for prilocaine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	183.00	5.00	0.84	14297.00	15492.00	7.71
102	120.00	5.00	1.00	27008.00	27818.00	2.91
103	162.00	5.00	0.97	32063.00	34474.00	6.99
105	118.00	5.00	0.97	32350.00	33638.00	3.83
201	135.00	5.00	0.98	15052.00	15726.00	4.29
202	156.00	5.00	0.90	17889.00	19213.00	6.89
203	160.00	5.00	0.94	18235.00	19520.00	6.58
204	343.00	5.00	0.92	13991.00	17230.00	18.80
205	153.00	5.00	0.94	25804.00	26807.00	3.74
206	141.00	5.00	0.97	43803.00	46764.00	6.33
207	193.00	5.00	0.93	28527.00	31416.00	9.20
Mean	169.45	5.00	0.94	24456.27	26190.73	7.03
SD	62.08	0.00	0.04	9499.34	9874.82	4.36
Min	118.00	5.00	0.84	13991.00	15492.00	2.91
Max	343.00	5.00	1.00	43803.00	46764.00	18.80

(Data source: Appendix 16.2.5. Table 2.11.1.)

Pharmacokinetic parameters for 2,6-xylidine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	350.00	5.00	0.89	2257.10	3484.45	35.22
102	310.73	5.00	0.94	6627.84	8702.30	23.84
103	1069.06	5.00	0.73	9001.98	24576.22	63.37
105	481.12	5.00	0.99	7024.08	13770.89	48.99
201	225.60	5.00	0.98	7722.62	9245.95	16.48
202	357.17	5.00	0.74	4168.94	6105.63	31.72
203	506.98	5.00	0.84	3237.49	5584.22	42.02
204	380.22	5.00	0.83	4156.60	6648.37	37.48
205	261.25	5.00	0.90	3654.53	4700.45	22.25
206	590.25	5.00	0.87	8384.35	17403.01	51.82
207	696.27	5.00	0.54	2945.87	7578.42	61.13
Mean	475.33	5.00	0.84	5380.13	9799.99	39.48
SD	242.81	0.00	0.13	2410.42	6368.70	15.63
Min	225.60	5.00	0.54	2257.10	3484.45	16.48
Max	1069.06	5.00	0.99	9001.98	24576.22	63.37

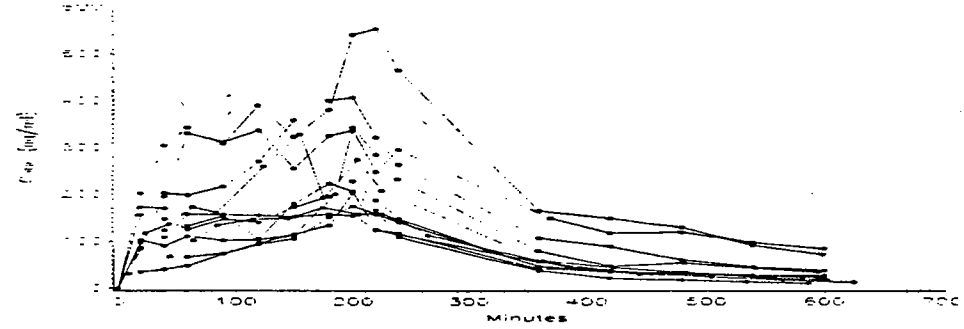
(Data source: Appendix 16.2.5. Table 2.13.1.)

Pharmacokinetic parameters for *o*-toluidine

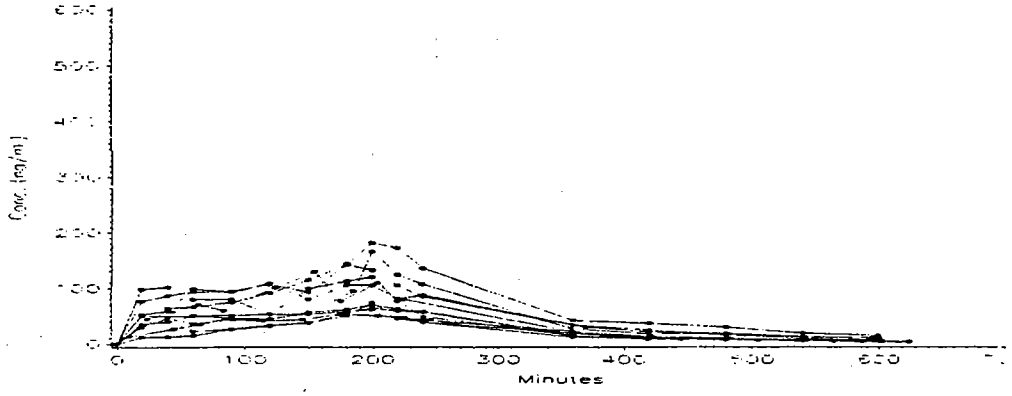
Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	231.00	5.00	0.92	4341.83	5598.06	22.44
102	291.00	5.00	0.96	8187.71	10618.75	22.89
103	268.00	5.00	0.97	15022.55	19248.22	21.95
105	219.00	5.00	0.89	9250.16	11719.37	21.07
201	147.00	5.00	1.00	6788.66	7286.02	6.83
202	260.00	5.00	0.87	4653.06	5924.37	21.46
203	313.00	5.00	0.79	4197.10	5717.77	26.60
204	273.00	5.00	0.97	6063.70	7729.01	21.53
205	121.00	5.00	0.97	4658.77	4973.06	6.32
206	192.00	5.00	0.95	11940.70	14347.63	16.78
207	338.00	5.00	0.43	5411.76	8051.14	32.78
Mean	241.36	5.00	0.88	7319.64	9201.22	20.06
SD	67.50	0.00	0.16	3513.93	4434.73	7.76
Min	121.00	5.00	0.43	4197.10	4973.06	6.32
Max	338.00	5.00	1.00	15022.55	19248.22	32.78

(Data source: Appendix 16.2.5. Table 2.14.1.)

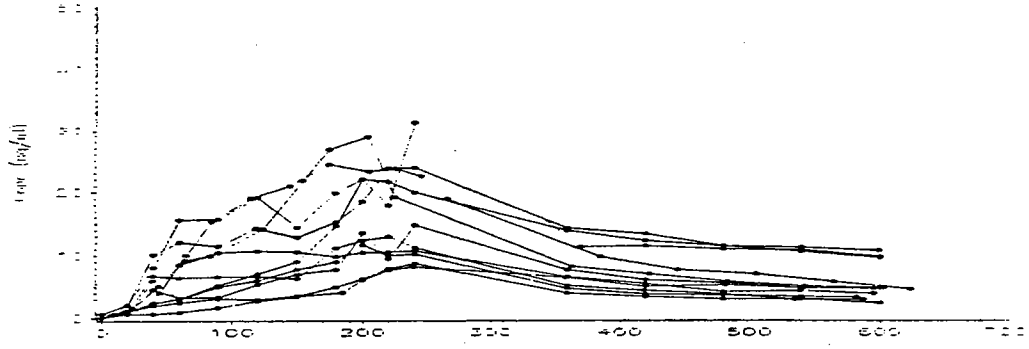
Lidocaine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5%:



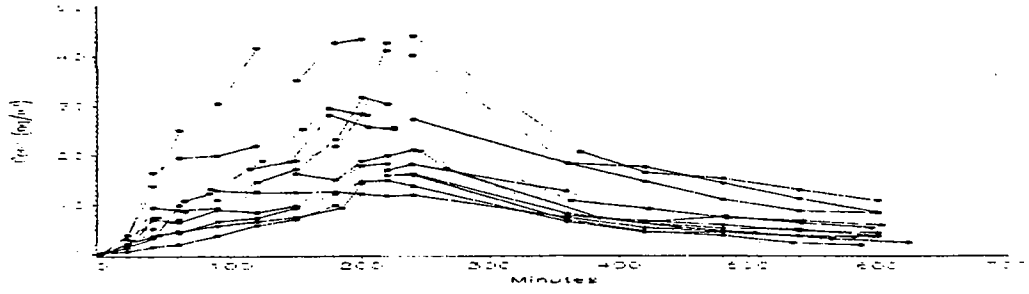
Prilocaine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5%



2,6-xylidine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5%

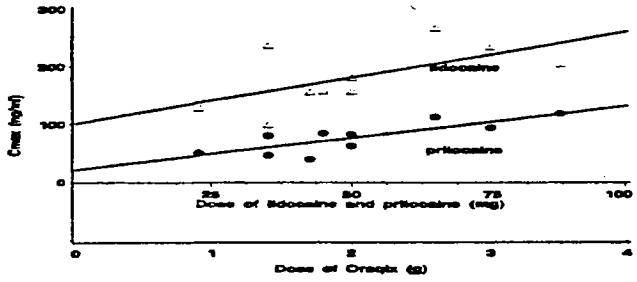


o-toluidine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5%



Does the Gel show lidocaine and prilocaine dose proportionality?

An analysis from Study A2 showed that lidocaine and prilocaine Cmax vs. dose seem to indicate a relationship between Cmax and dose administered, especially for the prilocaine. This study utilized 0.9 – 3.5 g Gel.



Individual C_{max} after administration of 0.9-3.5 g Periodontal Gel, corresponding to 22.5 to 87.5 mg each of lidocaine and prilocaine base, to all periodontal pockets in 10 patients requiring scaling and/or root planing [A2].

In the model used, the regression slope for ln(Cmax) vs. ln(dose) was statistically significantly different from zero for prilocaine (p=0.02), but not for lidocaine (p=0.0503).

4.3 Intrinsic Factors

Are there any gender differences observed?

No gender studies were conducted.

Are there any age differences observed?

The effect of age was not studied.

4.4 Extrinsic Factors

Does food affect the bioavailability of Gel?

No food effect studies were conducted.

4.5 General Biopharmaceutics

The Applicant stated that during the development of the Gel formulation, the stability tests showed that residual aldehydes present in poloxamers 188 and 407 reacted with prilocaine in the formulation. Thus a purification process for the poloxamers were developed. Gels used in pharmacokinetic studies A1 and A2 contained commercially available poloxamers whereas Gel used in pharmacokinetic study A3 contained purified poloxamers:

STUDIES	BATCH NUMBER	POLOXAMER
A1, A2	2415-3-2	Poloxamers 188 and 407 commercial grade NF
A3	2415-17-3	Poloxamers 188 and 407 purified

Additionally, there were three pivotal safety and efficacy clinical trials conducted in this NDA, B1, B2, and B3. Study B3 used to-be-marketed Gel formulation. The to-be-marketed Gel formulation contains purified poloxamers.

The Applicant presented the poloxamer characterization data comparing 'non-purified' and 'purified' poloxamers. The following methods were utilized in this characterization procedure:

1.
2.
3.

The data presented by the Applicant showed that the purified poloxamers will have the same physical and chemical properties as the non-purified poloxamers. Therefore, the release characteristics of the active ingredients should be similar for all Gels used in this drug product development. There should be no concern related to comparing the 'clinical' Gel formulation (non-purified poloxamers) to that of the to-be-marketed Gel formulation (purified poloxamers).

4.6 Analytical

Overall, the Applicant submitted adequate assay information (e.g., standard curves, QC's, validation results, etc.) There are no issues identified within the NDA submission regarding analytical procedures.

Typical assay information from A1, A2 and A3 Studies

for lidocaine and prilocaine, and the precision was — for lidocaine and — for prilocaine, with accuracies better than — and — respectively.

5 Labeling

The following proposal is recommended. The Applicant's proposal (Italics) is edited with ~~strikeouts~~, added, etc.

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

10 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

6.2 Individual Study Reviews

NDA 21-451 individual study reports

Appears This Way
On Original

STUDY A1

PROTOCOL TITLE:

A randomized parallel, open label study to evaluate the anesthetic onset time of lidocaine, prilocaine Oraqix for periodontal pocket anesthesia in conjunction with dental scaling and rootplaning (A1; Astra Report 802-544-LC-0007-01)

Summary critical to clinical pharmacology:

* In the 2 and 5 minute group, the highest individual plasma levels were 26.7 and 9.9 ng/ml for lidocaine and prilocaine, respectively, at 37 - 64 minutes after application of 0.1 - 0.7 g of Dental Gel 5 %; a single plasma sample was obtained at 37 – 64 min. post Gel application. These levels are below systemic pharmacological concentrations of lidocaine and prilocaine (approximately 1,000 – 1,200 ng/ml of either agent).

* In this study, patients who received the Dental Gel 5 % for 30 seconds before the SRP procedure commenced, had lower mean pain ratings than both the 2 minute and 5 minute application groups.

OBJECTIVES

The primary objective was to determine the onset time of anesthesia in the periodontal pocket provided by the Dental Gel 5%.

The secondary objectives were to determine the duration of action and adverse events associated with the application of Dental Gel 5 %, to investigate the handling properties and taste of the Dental Gel 5 % and to determine the plasma levels of lidocaine and prilocaine.

STUDY DESIGN

This was a parallel group, open, single center study with patients randomized to receive Dental Gel 5% for either 30 seconds, 2 minutes or 5 minutes prior to dental scaling and rootplaning (SRP). SRP commenced immediately after the allotted time period had expired (30 seconds, 2 or 5 minutes).

The duration of action of the Dental Gel 5% was measured by probing the pockets of each treated tooth at 5-minute intervals until an absence of anesthesia was recorded or until 30 minutes had passed.

An interruption of the SRP procedure due to pain was recorded for each tooth and the time at which this occurred was noted. Once an interruption occurred, the SRP procedure was not continued. If SRP was completed and the patient was still anaesthetized then the presence of anesthesia was checked every 5 minutes, using a dental probe, until sensation returned (or until 30 minutes had passed since the end of SRP). This intermittent probing was carried out whilst the next tooth was being treated.

All patients that were randomized to receive Dental Gel 5 % for 2 or 5 minutes had a blood sample taken (at 37-64 minutes after application of 0.1- 0.7 g of Dental Gel 5 %) after the SRP procedure has been completed and when all other assessments had been made. These samples were analyzed for plasma levels of lidocaine and prilocaine.

Possible adverse events were monitored throughout the treatment period and a follow up telephone call was made 24 - 48 hours after the treatment day to inquire about adverse events.

DRUG CONCENTRATION MEASUREMENTS

Collection and handling of blood samples

Those patients randomized to receive Dental Gel 5 % for 2 or 5 minutes had a blood sample taken after the SRP procedure had been completed and when all other assessments had been made. All blood and plasma tubes were labeled with specific labels provided by Astra.

Bioanalytical method

, and the precision was for lidocaine and for prilocaine, with accuracies better than and , respectively.

NUMBER OF PATIENTS (PLANNED AND ANALYSED)

Thirty per protocol patients were planned to be included in the study. A total of thirty patients, all per protocol, were included in the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients requiring SRP with a minimum of 2 teeth, and a maximum number of 4 teeth, were selected for treatment; each tooth had at least 1 periodontal pocket >6 mm in depth.

TEST DRUG, DOSAGE AND MODE OF ADMINISTRATION, BATCH NUMBER

Dental Gel 5% (batch number 2415-3-2), 0.1 g - 0.7 g, was delivered into the periodontal pocket by means of a syringe and blunt needle.

DURATION OF TREATMENT

Single dose

EFFICACY

The primary efficacy variable was the mean **Visual Analogue Scale (VAS)** pain score (the procedure was rated on a 100 mm visual analogue scale (VAS)) out of the total number of teeth scaled and rootplaned per patient (a minimum of 2 teeth and a maximum of 4 teeth). The secondary efficacy variables were pain assessment (the intensity of pain perceived by the patient during and a 5 point **Verbal Rating Scale (VRS)**), handling properties of Dental Gel 5 % and a taste assessment. At the end of the SRP procedure of each selected tooth.

SAFETY

Adverse events and plasma levels of lidocaine and prilocaine were measured.

STATISTICAL METHODS

Dental Gel 5 % application time groups were compared using mean VAS pain-score per patient as the primary variable. The other VAS pain score variables were considered as secondary. The comparisons were performed as two-sided 95 per cent confidence intervals estimating the group difference using a nonparametric method based on ranks corresponding to the Wilcoxon rank sum test.

The variables taste, VRS pain score, overall patient discomfort, overall ease of application and overall ease of scaling were summarized using frequency tables by application time groups and by tooth location.

The duration of action was summarized using standard descriptive statistics and further analyzed with a lifetest procedure with Kaplan-Meier survival estimates.

Note:

At the end of treatment after the patient had left the dental chair, the patient was asked to rate the overall discomfort felt during the procedure by using the following ratings: "no discomfort at all", "mild discomfort", "moderate discomfort", "severe discomfort" and "very severe discomfort", in response to the question "Rate the overall pain and distress from discomfort you felt from the application of anesthetic gel and the scaling/rootplaning procedure".

RESULTS AND CONCLUSION

1. Demographics

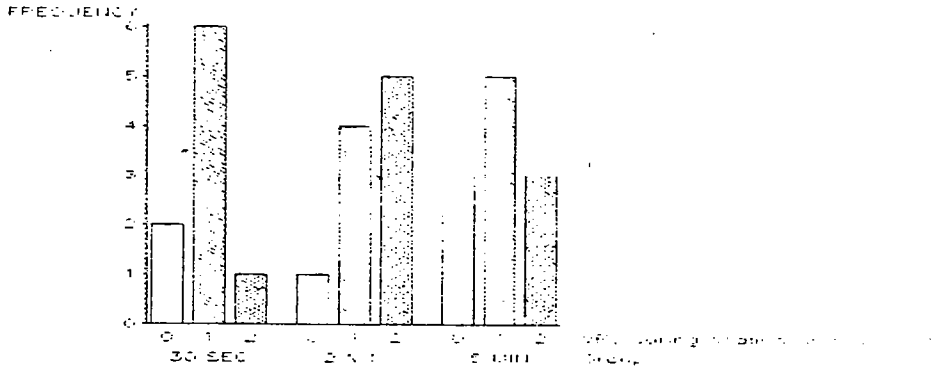
- Demographics

Group	n	Age (years) Median Mean ± sd	Sex M/F (n)	Weight (kg) Median Mean ± sd	Pocket depth (mm) Median Mean ± sd	Concurrent Medication (n)
30 sec	9	*47* 45 ± 8	2/7	68 71 ± 15	5 4.5 ± 1.7	2
2 min	10	*48* 46 ± 7	5/5	71 72 ± 8	4.5 4.6 ± 1.8	0
5 min	11	*53* *49* ± 9	3/8	75 80 ± 16	5 4.7 ± 1.8	3

2. EFFICACY RESULTS

Discomfort (overall)

The results of the VRS for patient discomfort from application of Dental Gel 5 % and SRP showed similar results for all application time groups. There were no scores for severe or very severe discomfort for any of the application time groups.



VRS patient discomfort during application/SRP
0 = no discomfort, 1 = mild discomfort, 2 = moderate discomfort
(No patient reported severe discomfort or very severe discomfort)

The results showed that the patients with an application time of 30 seconds felt less pain during the SRP procedure than the patients with longer application times. The group with an application time of 30 seconds had a statistically significant lower mean VAS score than the group with an application time of 2 minutes (p = 0.03).

Estimated mean of "Duration of Action" from end of administration for each group (Kaplan-Meier Estimates)

Group	Estimate (min)
30 sec	18.1
2 min	17.3
5 min	19.9

The estimated mean duration of action time was between 17 and 20 minutes. There was no significant difference in duration of action between the application time groups.

Efficacy conclusions

The results indicate that the patients with an application time of 30 seconds felt less pain during the SRP procedure than the patients with longer application times. The group with an application time of 30 seconds had a statistically significant lower VAS pain score than the group with an application time of 2 minutes.

The estimated mean duration of action, from pain on probing, was 17 - 20 minutes. There was no indication that the duration of action differed significantly between the application time groups.

SAFETY RESULTS

No local reactions were reported following a visual inspection of the gingiva after application of Dental Gel. No patient discontinued the study due to an adverse event. No serious adverse events were reported. Patient no 0011 reported minor pain in the mouth during Dental Gel 5 % application to each of the two teeth treated.

The plasma levels were below the limit of quantification (1 ng/ml) in one sample for lidocaine and in two samples for prilocaine. The highest individual plasma levels of lidocaine were 21.8 ng/ml and 26.7 ng/ml and the highest plasma levels of prilocaine were 9.9 ng/ml and 7.0 ng/ml in the 2 and 5 minute group respectively

Safety conclusions

Following single dose administration of 0.1 to 0.7 g Dental Gel 5 % into the periodontal pockets, the only adverse events reported were mild local effects of short duration.

For the 2 and 5 minute group, the highest individual plasma levels were 26.7 ng/ml for lidocaine and 9.9 ng/ml for prilocaine at 37-64 minutes after application of 0.1-0.7 g of Dental Gel 5 %.

Pharmacokinetic analysis

For the 2 and 5 minute group, the highest individual plasma levels were 26.7 ng/ml for lidocaine and 9.9 ng/ml for prilocaine at 37-64 minutes after application of 0.1- 0.7 g of Dental Gel 5 %.

Drug dose, drug concentration and relationships to response

Drug Dose

The total dose of Dental Gel 5 % given for all patients ranged from between 0.1 g and 0.7 g. The doses used were similar for each application time group and the number of teeth treated was either 2 or 3.

Total study dose - ml (1 ml ≡ 1.03 g)

All included patients

GROUP	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
30 SEC	9	0	0.27778	0.10929	0.2	0.2	0.2	0.3	0.5
2 MIN	10	0	0.27000	0.16364	0.1	0.2	0.2	0.3	0.7
5 MIN	10	1	0.23000	0.04830	0.2	0.2	0.2	0.3	0.3

Drug-drug and drug-disease interactions

There was no apparent relationship between response and concomitant treatment or between response and past/concurrent illness for any patient treated.

DISCUSSION AND OVERALL CONCLUSIONS

A. In this study, patients who received the Dental Gel 5 % for 30 seconds before the SRP procedure commenced, had lower mean pain ratings than both the 2 minute and 5 minute application groups.

B. Since the pain rating scores are higher in the 2 minute and 5 minute groups, it is likely that there is a limited anesthetic duration of Dental Gel 5%, although the Gel was contained in the periodontal pocket. One possible explanation for the limited anesthetic duration of Dental Gel 5% is the fairly rapid elimination of the lidocaine and prilocaine, which is probably accelerated by lidocaine/prilocaine-induced vasodilatation.

C. The Applicant stated that, from studies that EMLA ® cream was applied on the genital mucous membranes for thermocautery or CO2 laser treatment of genital warts (condylomata accuminata), the optimal degree of anesthesia was achieved after 5 -10 minutes application of EMLA ® Cream. In addition, surgical treatment initiated after longer applications than 10 - 15 minutes of EMLA ® Cream induced higher pain scores.

D. In the 2 and 5 minute group, the highest individual plasma levels were 26.7 ng/ml for lidocaine and 9.9 ng/ml for prilocaine at 37-64 minutes after application of 0.1 - 0.7 g of Dental Gel 5 %. These levels are below systemic pharmacological concentrations of lidocaine and prilocaine (approximately 1,000 – 1,200 ng/ml of either agent).

APPENDIX - Lidocaine and prilocaine concentrations

Group	Subject	Sampling date	Sampling time	Time since end of adm. (min)	Sampling nr	Drugcode		Concentration	Unit
30 SEC	0000002	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000003	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000009	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000013	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000015	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000016	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000023	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000026	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000030	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
2 MIN	0000001	1996-10-22	12:36	59	1	Prilocaine Tot conc		2	ng/mL
		1996-10-22	12:36	59	1	Lidocaine Total conc		7.8	ng/mL
	0000007	1996-11-08	09:49	51	7	Prilocaine Tot conc		2	ng/mL
		1996-11-08	09:49	51	7	Lidocaine Total conc		5.6	ng/mL
	0000008	1996-11-15	09:50	45	8	Prilocaine Tot conc		6.1	ng/mL
		1996-11-15	09:50	45	8	Lidocaine Total conc		21.8	ng/mL
	0000012	1996-11-20	10:01	48	12	Prilocaine Tot conc	<	1.1	ng/mL
		1996-11-20	10:01	48	12	Lidocaine Total conc		3.1	ng/mL
	0000017	1996-11-28	11:31	46	17	Prilocaine Tot conc		2.1	ng/mL
		1996-11-28	11:31	46	17	Lidocaine Total conc		6.2	ng/mL
	0000018	1996-11-29	12:07	60	18	Prilocaine Tot conc		2.2	ng/mL
		1996-11-29	12:07	60	18	Lidocaine Total conc		7.1	ng/mL
	0000024	1996-12-04	08:52	37	24	Prilocaine Tot conc		4.3	ng/mL
		1996-12-04	08:52	37	24	Lidocaine Total conc		9.6	ng/mL

Group	Subject	Sampling date	Sampling time	Time since end of adm. (min)	Sampling nr	Drugcode		Concentration	Unit
2 MIN	0000025	1996-12-05	11:20	46	25	Prilocaine Tot conc		4	ng/mL
		1996-12-05	11:20	46	25	Lidocaine Total conc		11.3	ng/mL
	0000027	1996-12-10	18:09	40	27	Prilocaine Tot conc		9.9	ng/mL
		1996-12-10	18:09	40	27	Lidocaine Total conc		17.9	ng/mL
	0000029	1996-12-16	11:28	58	29	Prilocaine Tot conc		5.8	ng/mL
		1996-12-16	11:28	58	29	Lidocaine Total conc		13.9	ng/mL
5 MIN	0000004	1996-11-06	10:13	64	4	Prilocaine Tot conc		3.7	ng/mL
		1996-11-06	10:13	64	4	Lidocaine Total conc		11.6	ng/mL
	0000005	1996-11-07	09:01	47	5	Prilocaine Tot conc		3	ng/mL
		1996-11-07	09:01	47	5	Lidocaine Total conc		9.3	ng/mL
	0000006	1996-11-08	09:13	53	6	Prilocaine Tot conc	<	1.1	ng/mL
		1996-11-08	09:13	53	6	Lidocaine Total conc	<	1.2	ng/mL
	0000010	1996-11-19	09:10	56	10	Prilocaine Tot conc		3.3	ng/mL
		1996-11-19	09:10	56	10	Lidocaine Total conc		24.3	ng/mL
	0000011	1996-11-19	14:12	51	11	Prilocaine Tot conc		2.1	ng/mL
		1996-11-19	14:12	51	11	Lidocaine Total conc		5.6	ng/mL
	0000014	1996-11-22	09:01	51	14	Prilocaine Tot conc		2.1	ng/mL
		1996-11-22	09:01	51	14	Lidocaine Total conc		7.1	ng/mL
	0000019	1996-12-02	11:25	56	19	Prilocaine Tot conc		3.5	ng/mL
		1996-12-02	11:25	56	19	Lidocaine Total conc		10.1	ng/mL
	0000020	1996-12-03	10:20	60	20	Prilocaine Tot conc		7	ng/mL
		1996-12-03	10:20	60	20	Lidocaine Total conc		16.7	ng/mL
	0000021	.P	.P	.	.P	Prilocaine Tot conc		.	ng/mL
		.P	.P	.	.P	Lidocaine Total conc		.	ng/mL
	0000022	1996-12-03	18:01	52	22	Prilocaine Tot conc		.	ng/mL
		1996-12-03	18:01	52	22	Lidocaine Total conc		.	ng/mL
	0000028	1996-12-12	11:24	51	28	Prilocaine Tot conc		3.9	ng/mL
		1996-12-12	11:24	51	28	Lidocaine Total conc		26.7	ng/mL

Omräknat till enheten ng/ml före data entry / GA 970226

DATA TABLE 1

PLASMA CONCENTRATIONS (nM) IN THE STUDY SAMPLES

Sample	Lidocaine (nM)	(ng/ml)	Prilocaine (nM)	(ng/ml)	Comments
1	33.4	7,8	9.3	2,0	
4	49.8	11,6	17.0	3,7	
5	39.9	9,3	13.7	3,0	
6	<5.0	<1,2	<5.0	<1,1	
7	23.7	5,6	8.9	2,0	
8	93.0	21,8	36.9	8,1	
10	104	24,3	14.8	3,3	
11	23.9	5,6	9.4	2,1	
12	13.2	3,1	<5.0	1,1	
14	30.3	7,1	9.6	2,1	
17	26.5	6,2	9.4	2,1	
18	30.4	7,1	9.9	2,2	
19	43.1	10,1	15.9	3,5	
20	71.4	16,7	31.6	7,0	
22	15.3	3,6	8.1	1,8	Total haemolysis
24	40.8	9,6	19.6	4,3	
25	48.2	11,3	18.2	4,0	
27	76.5	17,9	45.2	9,9	
28	114	26,7	17.8	3,9	
29	59.3	13,9	26.2	5,8	

MW lidocaine = 234 g mol^{-1}
MW Prilocaine = 220 g mol^{-1}

Study A2

Protocol Title

Pharmacokinetic evaluation of lidocaine and prilocaine in plasma following single-dose administration of lidocaine, prilocaine Oraqix to patients with widespread peridontal pockets requiring scaling/rootplaning. (A2 Astra Report 802-544-LC-0008-02 and 802-544-LC-0027-02)

Study Report 802-544-LC-0008-02 discusses lidocaine and prilocaine
Study Report 802-544-LC-0027-02 discusses 2,6-xylidine and o-toludine, metabolites of lidocaine and prilocaine, respectively.

Study Report 802-544-LC-0008-02

SUMMARY

PHARMACOKINETIC RESULTS

After a single application of Dental Gel 5% 0.9-3.5 g, peak plasma concentrations of lidocaine and prilocaine were 182 ± 53 (99-266) and 77 ± 27 (39-118) ng/ml, respectively. Peak plasma concentrations occurred 13-33 and 13-33 minutes post Dental Gel 5% periodontal pocket application. The data suggest that the Cmaxs of lidocaine (99-266 ng/ml) and prilocaine (39-118 ng/ml) were dependent on the dose, a result which was statistically significant for prilocaine.

EFFICACY RESULTS

The median VAS pain score during SRP, 14-27 minutes after the application of Dental Gel 5%, was 16.5 mm. The results suggest that the VAS pain score remain unchanged during the SRP of three consecutive teeth, 14-27 minutes after the start of application of Dental Gel 5%.

SAFETY RESULTS

Following a single dose of 0.9-3.5 g Dental Gel 5% in periodontal pockets, adverse events reported were mild local effects of short duration (e.g., a foul taste from the gel (n= 1), anesthesia of the throat or tongue due to overflow of Dental Gel 5% (n=2), pain or discomfort during application of the gel (n=2), a hematoma due to the blood sampling (n= 1), etc.).

STUDY OBJECTIVES

The primary objective was to establish the pharmacokinetic profiles in plasma of lidocaine and prilocaine following single-dose administration of Dental Gel 5% to patients with severe general periodontal disease.

The secondary objectives were to investigate Dental Gel 5% with reference to efficacy in terms of pain assessment during scaling and to assess safety.

INVESTIGATIONAL PLAN AND PROCEDURES

This single-center study was an open, descriptive trial evaluating the pharmacokinetics of lidocaine and prilocaine following a single dose of Dental Gel 5% in the periodontal pockets of patients with severe, generalized periodontal disease requiring SRP.

The patients were screened for eligibility according to the inclusion criteria and signed an informed consent form. A catheter for plasma sampling was inserted in a vein of the arm before the start of Dental Gel 5% application. Blood samples were taken before and 10, 20, 30, 40, 60,

75 and 90 minutes after the start of the Dental Gel 5% application for determination of the peak plasma concentrations of lidocaine and prilocaine.

The Dental Gel 5% was applied directly into the periodontal pocket by means of a blunt needle on all surfaces of all teeth. Following administration of Dental Gel 5% to all periodontal pockets of the mouth, probing of the periodontal pockets was performed on all the teeth, after which SRP was performed on three teeth.

Following the SRP of each tooth, the patient rated the pain experienced on a visual analogue scale (VAS). If the SRP of a tooth was interrupted due to pain, this was recorded and the SRP was discontinued. Following the SRP, the mouth was rinsed out with a glass of water. Adverse events were recorded during the study procedure and at a telephone follow-up 24 - 48 hours after the study procedure.

Study procedure / Flowchart

Insertion of catheter for blood sampling	Application of Dental Gel 5%	Probing	SPR (including pain assessment)	Rinsing with water
0	0-9	6-21	14-27	19-27
			Minutes (range) after start of appl. of Dental Gel 5%.	

Blood sampling took place 0, 10, 20, 30, 40, 60, 75 and 90 minutes after the start of application of Dental Gel 5%.

SELECTION AND TIMING OF DOSES FOR INDIVIDUAL PATIENTS

The dose regimen was chosen in order to maximize both the rate and the extent of absorption of the active substances lidocaine and prilocaine from Dental Gel 5%. The time of administration of the gel was as short as possible (6-9 minutes) and the gel was kept in the pockets as long as possible. The mouth was not rinsed out until the probing and SRP procedures were completed (9-27 minutes after the start of application of Dental Gel 5%).

PHARMACOKINETIC MEASUREMENTS AND VARIABLES

Collection and handling of blood samples

Bioanalytical method

. The limit of quantitation was ng/ml) for lidocaine and prilocaine and the precision was for lidocaine and for prilocaine, with accuracies exceeding and respectively.

Pharmacokinetic parameters

The pharmacokinetic evaluation was performed according to non-compartmental model-independent analysis. The peak plasma level (Cmax) and the time to reach Cmax (tmax) were obtained directly from the observed plasma levels for lidocaine and prilocaine respectively. The area under the plasma concentration time curve up to the last sampling time (AUCt) was determined by means of the trapezoidal rule.

APPROPRIATENESS OF MEASUREMENTS

Statistical methods and determination of sample size

STATISTICAL EVALUATION

The SAS system, version 6.11, was used for the statistical analysis. The pharmacokinetic variables as well as efficacy and background variables were summarized using standard descriptive statistics such as mean, standard deviation, minimum and maximum values and median. Adverse events were listed by patient.

Scatter plots of the lidocaine/prilocaine C_{max} vs the dose given were made to investigate the dependence between dose and C_{max}. In addition, to carry out a more formal test of dependence, the following general linear model was applied (4) :

$$\ln(C_{max_i}) = \alpha + \beta \ln(dose_i) + \varepsilon_i ,$$

where α is the intercept, β is the regression slope and ε_i is a random error. This model can be rewritten as

$$C_{max\,i} = \alpha' dose_i^{\beta} \varepsilon'_i ,$$

where $\alpha' = e^{\alpha}$ and $\varepsilon'_i = e^{\varepsilon}$.

Written in this form, this model has the property $dose=0 \Rightarrow C_{max}=0$. If the dose is doubled, then C_{max} increases by a factor of 2^{β}.

DOSE, PROBING AND SCALING PROCEDURES

The patients had 18-28 teeth with pocket depths of at least 4 mm. An amount of 0.9-3.5 g of Dental Gel 5% was applied to the pockets around all the teeth, which is equivalent to 0.08 + 0.03 (0.05-0.13) g around each tooth. Thereafter probing of all teeth was completed within 9-14 minutes and SRP was completed for three teeth within 3-9 minutes. SRP was performed 16-27 minutes after the start of administration of Dental Gel. Following the probing and SRP procedures, 19-27 minutes after the start of application, the mouth was rinsed out with a glass of water

RESULTS

1. Demographics

Eleven male and female Caucasians in the age group 38 - 56 years were included in the study. Six of the patients were smokers, two were previous smokers, one used snuff and two were nonsmokers. All the patients had a normal general appearance of the oral cavity and a normal general appearance.

None of the patients received any concomitant medication during the study procedure. Patient #103 received Calciopen (phenoxymethylpencillin) for ten days but completed the treatment four days before the study procedure.

Demographics

Pat #	Age (years)	Sex (M/F)	Weight (kg)	Height (cm)	Smoking habits
101	41	F	60	165	S
102	43	M	80	169	S
103	56	F	65	166	S
104	45	F	65	162	S
105	39	F	63	164	-
106	45	F	68	155	S
107	52	F	72	171	PS
108	46	F	73	172	PS
109	38	M	90	190	S
110	50	F	85	170	-
111	52	M	100	185	- Snuff
x ± sd	46 ± 6	3 M	75 ± 13	170 ± 10	
median	45	8 F	72	169	
(range)	(38-56)		(60-100)	(155-190)	

S = habitual smoker, - = Nonsmoker, PS = previous smoker

2. Dose, probing and scaling timelines

Dose, probing and scaling timelines

Pat #	No. of teeth with pockets ≥ 4 mm	Total amount of Dental Gel (g)	Adm of Dental Gel time (min)	Probing time* (min)	SRP time (min)	Time (min) before rinsing
101	28	1.8	7	10	9	26
102	26	2.0	7	14	4	25
103	18	0.9	7	8	7	22
104	23	1.4	7	8	5	20
105	24	1.4	7	8	6	21
106	25	2.0	7	10	7	24
107	24	1.9	6	12	1	19
108	25	1.7	6	9	5	20
109	26	3.5	9	10	8	27
110	24	3.0	7	7	9	23
111	21	2.6	8	10	8	26
x ± sd	24 ± 2.7	2.0 ± 0.8	7 ± 0.8	9.6 ±2.0	6.3± 2.4	23 ± 2.8
median	24	1.9	7	9.5	7	23
(range)	(18-28)	(0.9-3.5)	(6-9)	(7-14)	(1-9)	(19-27)

* Probing time was calculated as: Time from end of administration of Dental Gel 5% until start of SRP.

3. Pharmacokinetic results

C_{max}, $t_{max\ start}$ and $t_{max\ end}$ for lidocaine and prilocaine.

	Lidocaine			Prilocaine		
Pat #	C_{max} (ng/ml)	$t_{max\ start}$ (min)	$t_{max\ end}$ (min)	C_{max} (ng/ml)	$t_{max\ start}$ (min)	$t_{max\ end}$ (min)
101	157	40	33	84	40	33
102	157	30	23	82	30	23
103	127	30	23	50	30	28
104	99	30	23	46	30	23
105	236	20	13	80	20	13
106	181	30	23	62	30	23
108	156	30	24	39	30	24
109	204	30	21	118	30	21
110	234	30	23	94	30	23
111	266	40	32	112	30	32
x ± sd	181.7 ± 52.7	31 ± 5.68	23.8 ± 5.57	76.7 ± 27.2	30.0 ± 4.71	24.3 ± 5.72
median	169	30	23	81	30	23
(range)	(99-266)	(20-40)	(13-33)	(39-118)	(20-40)	(13-33)

$t_{max\ start}$ = tmax from start of administration of Dental Gel 5%
$t_{max\ end}$ = $t_{max\ start}$ - time of administration of Dental Gel 5%

AUCt, AUC∞ and residual (% of AUC∞) for lidocaine and prilocaine.

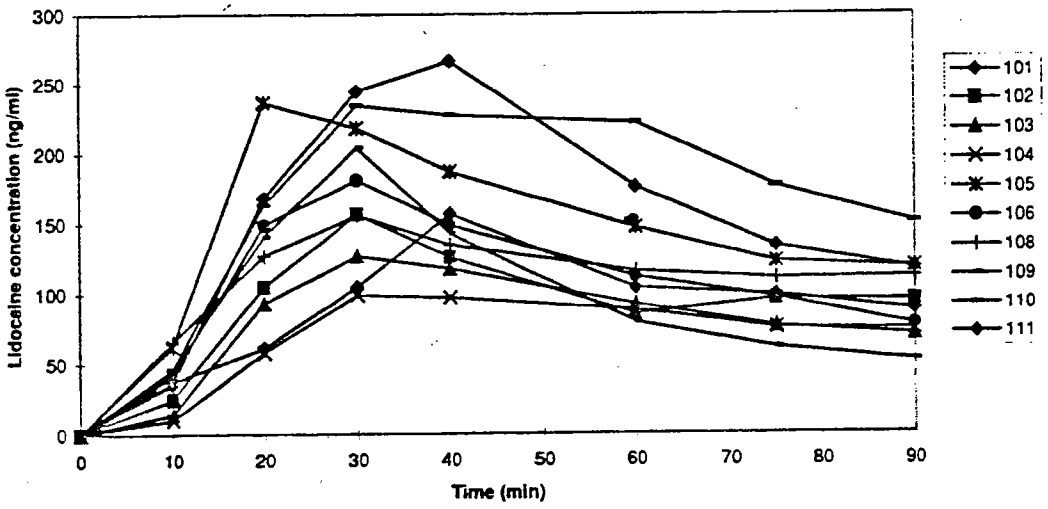
	Lidocaine			Prilocaine		
Pat #	AUCt (ngmin/ml)	AUC∞ (ngmin/ml)	residual (% of AUC∞)	AUCt (ngmin/ml)	AUC∞ (ngmin/ml)	residual (% of AUC∞)
101	8 350	19557	57	4 195	8806	52
102	8 205	144291	94	3 900	-	-
103	7 385	20153	63	3 212	9244	65
104	6 345	89039	93	2 548	-	-
105	13 275	67266	80	3 778	-	-
106	9 938	14940	33	3 235	4280	24
108	10 040	-	-	2 332	6830	66
109	8 722	13609	36	5 012	6798	26
110	15 508	29764	45	4 950	11556	57
111	14 435	28355	49	5 302	8441	37
x ±	10 220 ±	47 442 ±	61±	3 846 ±	7994 ±	47±
sd	3 127	44 586	23	1 032	2298	18
median	9330	28 355	57	3 839	8441	52
(range)	(6345-15508)	(13 609-144 291)	(33-94)	(2 332-5 302)	(4280-11556)	(24-66)

The mean peak plasma concentration (Cmax) was 181.7 ± 52.7ng/mL (range 99-266 ng/mL; individual lidocaine plasma levels were from 10 to 266 ng/mL). The mean areas under the plasma concentration-time curve from time 0 to the last sampling time (AUCt) for lidocaine was 10,220 ± 3,127 ng.min/mL.

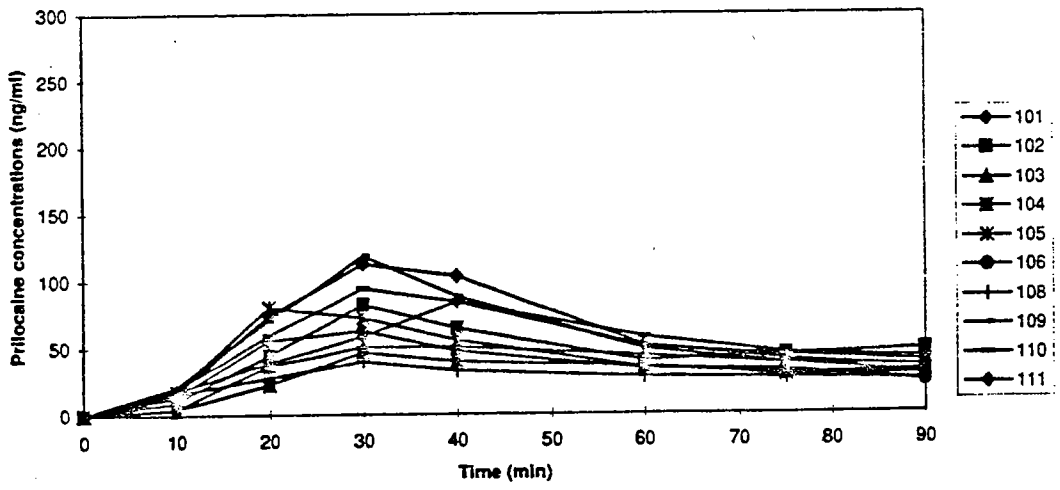
Prilocaine plasma levels were lower than lidocaine plasma levels. The mean peak plasma concentration (Cmax) was 76.7 ± 27.2 ng/mL (range 39-118 ng/mL). The mean areas under the plasma concentration-time curve from time 0 to the last sampling time (AUCt) for prilocaine was 3,846 ± 1,032 ng.min/mL.

Cmax was reached in all patients 20 to 40 minutes after the start of application of Dental Gel 5% and 13-33 minutes after the gel was applied in the pockets.

Lidocaine plasma levels following administration of Dental Gel 5%

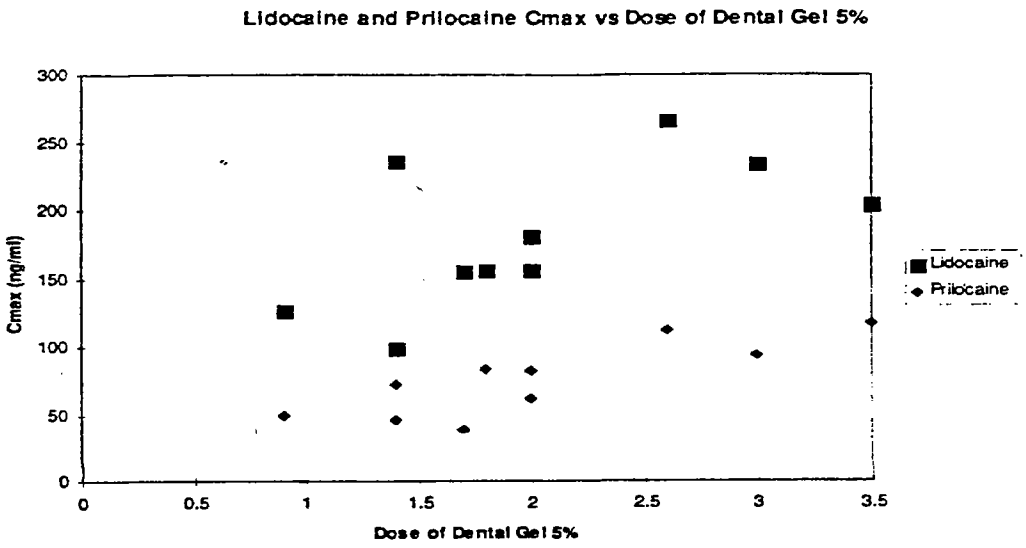


Prilocaine plasma levels following administration of Dental Gel 5%



DRUG CONCENTRATION AND RELATIONSHIPS TO DOSE

The scatter plots of lidocaine and prilocaine Cmax vs dose indicate a dependence between Cmax and dose administered.



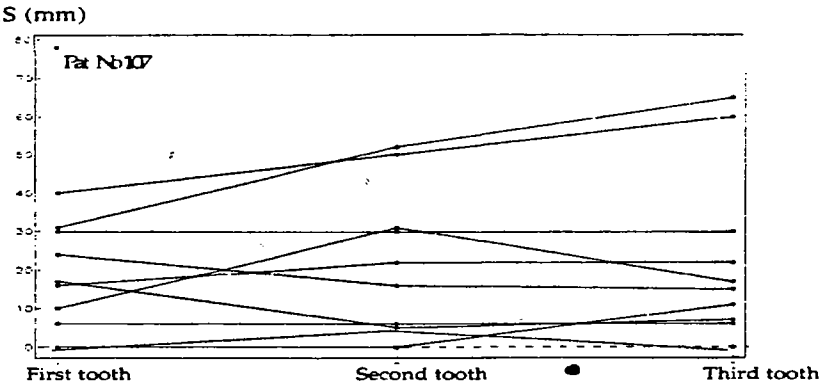
In the model used, the regression slope for ln(Cmax) vs ln(dose) was statistically significantly different from zero for prilocaine (p=0.02), but not for lidocaine (p=0.0503). In the linear regression, about 53% of the variance in Cmax for prilocaine could be explained by the dose given. The corresponding value was 40% for lidocaine. Using this model, Cmax-values for prilocaine and lidocaine are estimated to increase by factors of 1.6 and 1.4 respectively when the dose of Dental Gel 5% is doubled.

4. EFFICACY AND SAFETY EVALUATION

Efficacy evaluation

In one of the patients (Pat #107), the SRP procedure was interrupted due to pain during scaling of the first tooth. The VAS pain score recorded for this tooth was 78 mm. In the remaining ten patients pain was assessed following the scaling of three teeth. The median VAS pain scores were 16.5, 19 and 16 mm following scaling of the first, second and third teeth, and the overall median VAS pain score was 16.5 mm in these patients.

In the descriptive statistics no major differences in VAS pain score for the three teeth scaled was observed. The pain scores were similar during the time required for SRP (3-9 minutes) within the interval 14 to 27 minutes after the start of application of Dental Gel 5%.



VAS (mm) pain score following SRP of three consecutive teeth.

The results suggested that the VAS pain score remains unchanged during the SRP of three consecutive teeth 14-27 minutes after the start of application of Dental Gel 5%.

ADVERSE EVENTS

Brief summary of adverse events

Six adverse events of mild or moderate intensity were reported in 5 of the patients. Patient # 105 experienced a foul taste from the gel. Patients (Pat #107 and 108) were anesthetised in the throat or tongue due to overflow of the gel. Patients (Pat #102 and 110) experienced pain or discomfort during application of the gel, and one patient (Pat #102) had a hematoma in the right arm due to the blood sampling. The first three AEs were considered to be related to the study drug.

Adverse events displayed as Preferred Term by System Organ Class

	Dental Gel 5% (n=11)	
System organ class	Patients with adverse events	
Preferred Term	n	(%)
Special senses other, disorders		
Taste perversion	1	9
Platelet, bleeding & clotting disorders		
Bleeding post-vessel puncture	1	9
Application site disorders		
Application site reaction	2	18
Anesthesia local	2	18

DISCUSSION AND OVERALL CONCLUSION

A. The Applicant stated that the absorption of lidocaine and prilocaine from EMLA® cream into the systemic circulation has been documented for intact skin and genital and gingival mucosae. Following application of 10 g EMLA® cream to the face for 2 hours, mean maximum levels of lidocaine and prilocaine, 150 ng/mL and 58 ng/mL respectively, were reached after 1.5-3 hours. Peak plasma concentrations of lidocaine and prilocaine following application of 10 g EMLA® cream for 10 minutes to genital mucosa, 180 ng/ml and 150 ng/ml, were reached after 20-45 minutes. The application of 4 g EMLA® cream for 4 minutes to the gingival mucosa in 25 patients resulted in maximum individual Cmax values of 470

ng/ml (5 minutes after application) and 2 I0 ng/ml (10 minutes after application) for lidocaine and prilocaine respectively. Initial symptoms of CNS toxicity would be expected to occur at 5000-6000 ng/ml.

B. In the current study, the doses administered ranged from 0.9 to 3.5 g Dental Gel 5%, corresponding to 0.05-0.13 g Dental Gel 5% per tooth.

C. Peak plasma concentrations of both lidocaine and prilocaine were reached within 33 minutes after Dental Gel 5% had been applied in periodontal pockets.

D. In general, the plasma levels of prilocaine were lower than those of lidocaine.

E. Cmax for lidocaine was 182 ± 53 (99-266) ng/ml and Cmax for prilocaine was 77 ± 27 (39-118) ng/ml. Cmax tended to be dependent on the dose administered, as expected. For prilocaine, Cmax was statistically significantly related to dose, about 50% of the variance in Cmax being explainable by dose.

F. The results from this study indicate that the VAS pain score remained unchanged during SRP of three consecutive teeth 16-27 minutes after the start of application of Dental Gel 5%.

Study A2 Metabolite Study

Protocol Title

Pharmacokinetic evaluation of lidocaine and prilocaine in plasma following single-dose administration of lidocaine, prilocaine Oraqix to patients with widespread peridontal pockets requiring scaling/rootplaning (A2 Astra Report 802-544-LC-0008-02 and 802-544-LC-0027-02)

Study Report 802-544-LC-0008-02 discusses lidocaine and prilocaine.
Study Report 802-544-LC-0027-02 discusses 2,6-xylidine and o-toludine, metabolites of lidocaine and prilocaine, respectively.

STUDY REPORT 802-544-LC-0027-02

INTRODUCTION

Dental Gel 5% consists of the active ingredients lidocaine and prilocaine in the same concentrations as in EMLA® cream 5%. The information on the plasma levels of the lidocaine metabolite 2,6-xylidine is scanty due to lack of sensitivity of the analytical methods available. The plasma levels of 2,6-xylidine and o-toluidine have been determined following repeated administration of 2-10 g EMLA® cream 5% to patients with venous leg ulcers. In a majority of the samples the plasma levels of 2,6-xylidine and o-toluidine were below both the levels of their parent compounds and the limit of quantification (LOQ) of the liquid chromatography/mass spectrometry method (LC/MS) used, 50 nmol/l and 10 nmol/1 for 2,6-xylidine and o-toluidine respectively. Thereafter, the sensitivity of the LC/MS method has been improved with respect to 2,6-xylidine and o-toluidine.

The present study was designed to evaluate the systemic exposure of lidocaine and prilocaine following single dose administration of Dental Gel 5% to patients with severe, generalized periodontal disease requiring scaling/rootplaning (SRP). These results are reported in the Clinical Report 802-544-LC-0008. In order to increase the knowledge of the pharmacokinetics of 2,6-xylidine and o-toluidine, additional exploratory analyses of the plasma levels of these metabolites were performed in this study.

Demographic and other baseline characteristics

Eleven male and female Caucasians in the age group 38 - 56 years were included in the study. Six of the patients were smokers, two were previous smokers, one used snuff and two were nonsmokers. All the patients had a normal general appearance of the oral cavity and a normal general appearance.

Demographics

Pat #	Age (years)	Sex (M/F)	Weight (kg)	Height (cm)	Smoking habits
101	41	F	60	165	S
102	43	M	80	169	S
103	56	F	65	166	S
104	45	F	65	162	S
105	39	F	63	164	-
106	45	F	68	155	S
107	52	F	72	171	PS
108	46	F	73	172	PS
109	38	M	90	190	S
110	50	F	85	170	-
111	52	M	100	185	- Snuff
x ± sd median (range)	46 ± 6 45 (38-56)	3 M 8 F	75 ± 13 72 (60-100)	170 ± 10 169 (155-190)	

S = habitual smoker, - = Nonsmoker, PS = previous smoker

CONCLUSIONS

Following application of Dental Gel 5% 0.9-3.5 g in periodontal pockets, Cmax values of the lidocaine metabolite 2,6-xylidine and the prilocaine metabolite o-toluidine were in the range 13-117 nmol/L and 48-146 nmol/L, respectively. These values do not exceed 15% and 50% of lidocaine and prilocaine Cmax values respectively in any of the individuals. Tmax for the metabolites were reached 60-75 minutes and 60-90 minutes after start of application of Dental Gel 5% for 2,6-xylidine and o-toluidine, respectively. The plasma levels of 2,6-xylidine and o-toluidine were in general lower than for lidocaine and prilocaine, respectively.

The sensitivity of the LC/MS method used was improved since earlier studies. Limits of quantitation at for 2,6-xylidine and o-toluidine, respectively, made it possible to quantify the plasma levels of these metabolites. The quantifiable plasma levels were between for 2,6-xylidine and between nd for o-toluidine.

The ratio of Cmax 2,6-xylidine/Cmax lidocaine was in the range 0.01-0.15 and the ratio of Cmax o-toluidine / Cmax prilocaine was between 0.12 and 0.48. Tmax for 2,6-xylidine and o-toluidine was larger than for their parent compounds.

Appendix I

INTRODUCTION

This is a validation report of the bioanalytical method no. B-0020-01.

VALIDATION PROCEDURE

The validation study was performed on three occasions, 970828, 970908 and 970916. Since this method only will be used for minor studies where all samples can be analyzed in a short period of time, no in-between days validation was performed.

SELECTIVITY

No significant peaks interfering with o-toluidine or 2.6-xylidine were observed in the chromatograms obtained from the blank matrixes.

LIMIT OF QUANTIFICATION, LOQ

The limit of quantification was set of o-toluidine and of 2.6-xylidine.

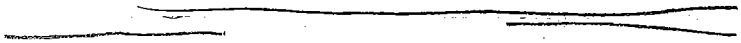
TEST DRUG, DOSAGE AND MODE OF ADMINISTRATION, BATCH NUMBER

Dental Gel 5%, 0.9-3.5 g, was applied into the periodontal pockets around all the teeth. Thereafter probing was performed on all teeth and scaling/rootplaning was performed on three teeth. Batch number 2415-3-2 was used.

PHARMACOKINETIC MEASUREMENTS AND VARIABLES

Collection and handling of blood sample

Bioanalytical method



The precision for 2,6-xylidine was better than — with an accuracy of — and the precision for o-toluidine was better than — with an accuracy of — The LOQ were — for 2,6-xylidine and 9.4 nmol/L for o-toluidine using 500 µL plasma.

Pharmacokinetic parameters

The pharmacokinetic evaluation was performed according to non-compartmental analysis. The peak plasma level (Cmax) and the time to reach Cmax (tmax) were obtained directly from the observed plasma levels for 2,6-xylidine and o-toluidine, respectively.

Appropriateness of measurements

The LC/MS method used was adequate for determination of 2,6-xylidine and o-toluidine in most samples. The plasma levels were not quantifiable in 18 samples and in 12 samples on the rising part of the plasma curves due to insufficient sensitivity of the method for 2,6-xylidine and o-toluidine respectively. The plasma levels were above LOQ in all samples in the declining part of the plasma curves.

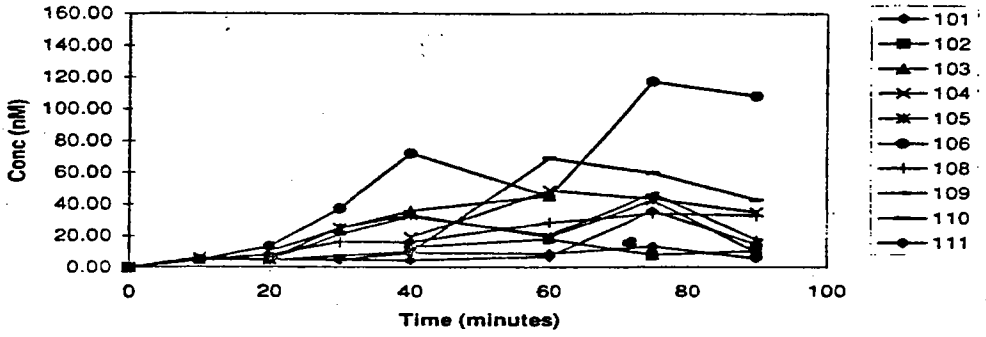
The blood sampling schedule was adequate for identification of Cmax and tmax values in all but one patient (Pat #101). Since the highest observed plasma level of o-toluidine was reached in the last sample, 90 minutes after application, additional samples would have been necessary.

PHARMACOKINETIC RESULTS

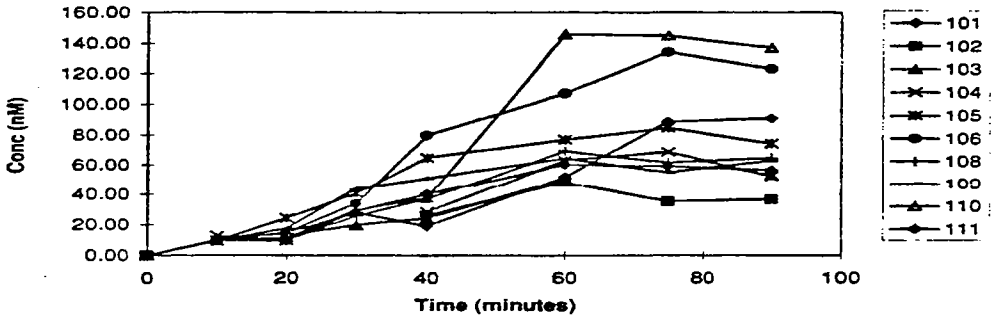
Individual Cmax values were 13-117 nmol/L for 2,6-xylidine and 48-146 nmol/L for o-toluidine occurring 60-75 and 60-90 minutes after application, respectively. The molar ratio of Cmax 2,6-xylidine/Cmax lidocaine was in the range 0.01-0.15, and the ratio of Cmax o-toluidine/Cmax

prilocaine was between 0.12 and 0.48. The plasma levels of 2,6-xylidine and o-toluidine were lower and Cmax was reached later than for their parent compounds.

Plasma concentrations of 2,6-xylidine



Plasma concentrations of *O*-toluidine



C_{max} and t_{max} for lidocaine, 2,6-xylidine, prilocaine and *o*-toluidine

	C_{max} (nmol/l) x ± sd (range)	t_{max} (min) median (range)
Lidocaine	777 ± 225 (421-1137)	30 (20-40)
2,6-xylidine	47 ± 29 (13-117)	75 (60-75)
Prilocaine	348 ± 123 (176-536)	30 (30-40)
o-toluidine	82 ± 33 (48-146)	67.5 (60-90)

Ratio C_{max} 2,6-xylidine/ C_{max} lidocaine, C_{max} *o*-toluidine / C_{max} prilocaine

Pat #	C_{max} 2,6-xylidine/ C_{max} lidocaine	C_{max} *o*-toluidine / C_{max} prilocaine
101	0.05	0.24
102	0.03	0.13
103	0.08	0.23
104	0.12	0.33
105	0.04	0.23
106	0.15	0.48
108	0.05	0.39
109	0.05	0.12
110	0.07	0.34
111	0.01	0.12
x ± sd (range)	0.07 ± 0.04 (0.01-0.15)	0.26 ± 0.12 (0.12-0.48)

STABILITY IN PLASMA

The freeze-thaw stability study of o-toluidine and 2.6-xylidine in human plasma consisted in freezing the quality control samples prior to analysis. No significant instability was seen.

CALIBRATION RANGE

The calibration range was tested within the concentration range 9.4-226 nmol/1 of o-toluidine and 4.6-111 nmol/1 of 2.6-xylidine, using 500 µL of plasma.

ACCURACY AND PRECISION

— limit of quantification, —low quality control samples, —medium quality control samples and — high quality control were analyzed simultaneously. The calculated concentrations of the quality control samples were . ——— and the RSD were in most cases below ———

RECOVERY

The recovery of the substances were studied through analysis of reference standard solution without plasma and without ultra filtration compared to ultra filtrated standard solution in plasma. Further, the recovery on the pre-column was studied by comparison of injection of pure standard solutions on the pre-column compared to direct injection on the analytical column. Since the sensitivity of the mass spectrometer increased during the analysis it's difficult to calculate the recovery, but the recovery for the substances were estimated to be high. No loss of the substances were seen on the pre-column after injection of more than two hundred samples with a volume of —

CONCLUSIONS

The validation data shows that the new method B-0020-01 is suitable for the determination of o-toluidine and 2.6-xylidine in human plasma.

1 Page(s) Withheld

6 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2

STUDY A3

PROTOCOL TITLE:

Pharmacokinetic evaluation of lidocaine, prilocaine, 2,6-xylidine and o-toluidine in plasma following administration of lidocaine, prilocaine Dental Gel 5% to patients with widespread periodontal disease subjected to probing and scaling/rootplaning (A3; AstraZeneca Report 802-544-LC-0037-01)

OBJECTIVES

The primary objective was to evaluate the plasma profiles of lidocaine, prilocaine, 2,6-xylidine, and o-toluidine following administration of 8.5 g (5 cartridges) Dental Gel 5% to patients with widespread periodontal disease, subjected to probing and scaling/rootplaning (SRP).

The secondary objectives were to evaluate tolerability, including Metlib blood level determination, to evaluate efficacy, and to compare the pocket depth assessment before and after application of Dental Gel 5%.

STUDY DESIGN

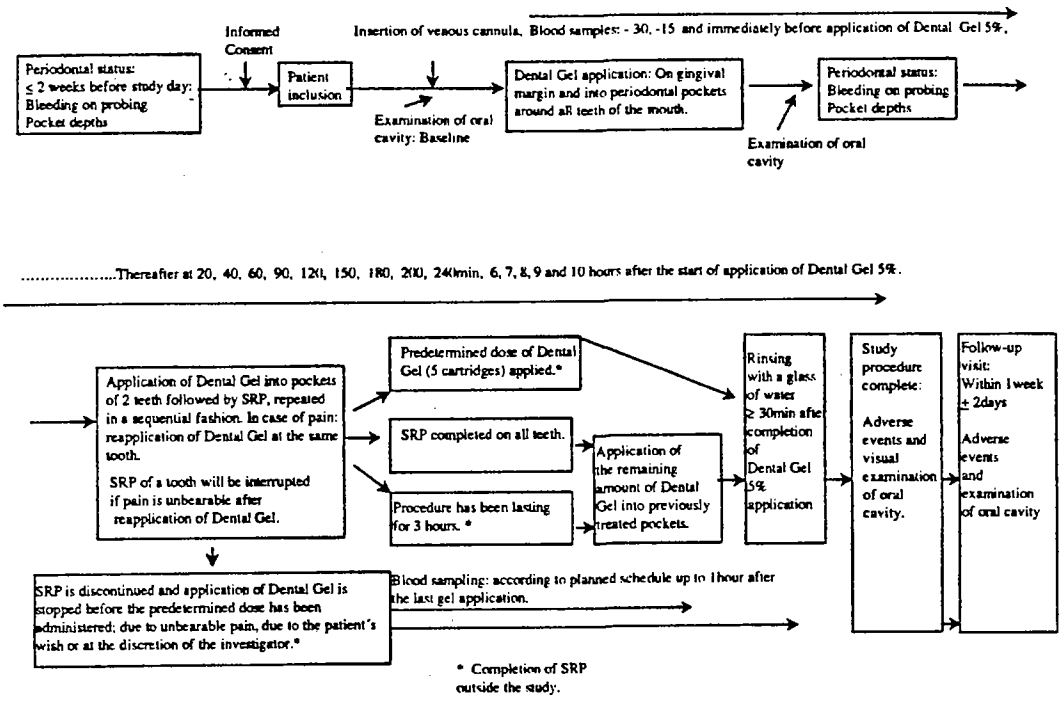
This two-center study was an open, descriptive trial evaluating the pharmacokinetics of lidocaine, prilocaine, 2,6-xylidine, and o-toluidine following a single dose of Dental Gel 5% in the periodontal pockets of patients with widespread periodontal disease requiring SRP.

The study comprised one study day and a follow-up visit one week +2 days after the study day. The patients were screened for eligibility according to the inclusion criteria and signed informed consent before being included in the study. The assessment of pocket depths was performed in the four weeks before the study day. Before application of Dental Gel 5%, a baseline inspection of the oral cavity was performed and a venous catheter was inserted. Venous blood samples were taken 15 and 30 min before, and immediately before and 20, 40, 60, 90, 120, 150, 180, 200, 220, and 240 minutes, 6, 7, 8, 9, and 10 hours after the start of application of the gel. Metlib levels were determined in all samples, while the levels of lidocaine, prilocaine, 2,6-xylidine, and o-toluidine were determined in all samples except those taken 30 and 15 min before application.

Dental Gel 5% was administered by means of a standard 1.8-mL dental cartridge system with a blunt 23-G applicator. Five cartridges of Dental Gel 5% were administered to each patient. The exact amount of Dental Gel 5% administered was measured by weighing the cartridges and syringes before the start of administration of Dental Gel 5% and at the end of the gel application. The gel was applied at the gingival margin around all the teeth of the mouth. Directly thereafter Dental Gel 5% was applied to the periodontal pockets of all the teeth, followed by periodontal probing to assess the periodontal pocket depths and bleeding on probing on all teeth.

Thereafter the gel was applied to the periodontal pockets of two teeth, followed by adequate SRP of these teeth. In case of pain from SRP, reapplication was allowed. The application of gel and SRP was repeated until all the teeth had been completed or until the predetermined dose of Dental Gel 5% had been applied, or up to 3 hours after the start of application of Dental Gel 5%. If some of the predetermined dose of Dental Gel 5% still remained after completing SRP of all teeth or at 3 hours after the start of application of the gel, the remaining gel was applied to the previously treated periodontal pockets. The SRP was interrupted if the predetermined dose of Dental Gel 5% was used up before the SRP had been completed for all teeth. During the procedures excess saliva was removed by suction when required. Expectoration was allowed during the study procedure, although the patient was not allowed to rinse his/her mouth with a glass of water until half an hour after the application of Dental Gel 5% was complete. In case of an uncomfortable dry mouth, the mucous membranes were sprayed with water.

Flow Chart SP-DGA-0006



Dosing

Based on the findings of previous studies, on average one cartridge of Dental Gel 5% is needed for SRP of one quadrant. The proposed maximum total recommended dose, including re-applications, on each occasion of treatment will be 8.5g, i.e., five cartridges of Dental Gel 5%, corresponding to 212.5mg each of lidocaine and prilocaine base. The present study was aiming at documenting the systemic safety of five cartridges of Dental Gel 5%.

PK Sampling

A catheter was inserted in a vein before the start of application of Dental Gel 5%. Blood samples were collected 15 and 30 minutes before and immediately prior to gel application and at 20, 40, 60, 90, 120, 150, 180, 200, 220, and 240 minutes and 6, 7, 8, 9, and 10 hours after the start of application of Dental Gel 5%. A volume of 0.5 mL was discarded before collection of the actual blood sample. Metlib levels were determined in all blood samples, while the levels of lidocaine, prilocaine, 2,6-xylidine, and o-toluidine were determined in all samples except those taken 30 and 15 minutes before application. The blood samples for Metlib determination (0.5-1.0 mL) were

then stored in a freezer at -20°C until drug assay. The exact time of blood sampling was recorded on the CRF.

Bio-analytical methods

. The limits of quantitation (LOQ) were for lidocaine, prilocaine, and o-toluidine and for 2,6-xylidine. The precision was for prilocaine, % for lidocaine, for 2,6-xylidine, and for o-toluidine. The accuracies were between and for all analytes studied.

Pharmacokinetic evaluation

Noncompartmental analysis was used to estimate the individual pharmacokinetics of lidocaine, prilocaine, 2,6-xylidine, and o-toluidine using software The peak plasma level (Cmax) and time to reach Cmax (tmax) were obtained directly from the observed plasma levels. The area under the plasma-concentration time curve up to the last sampling time (AUCt) and the area under the plasma concentration versus time curve from time zero to infinity (AUCinf) were calculated. AUC was calculated using the linear trapezoidal rule, with extrapolation to infinity. Plasma levels below the LOQ appearing in terminal samples were omitted from the analysis. The terminal half-life (tl/2 Z) was calculated as ln2/kz.

Laboratory safety measurements, and variables

The Metlib values were determined Metlib levels were measured as the total amount of Hb available as Metlib (0.0-100.0 %). The reference value for Metlib is <2%. had a precision of (95% confidence interval) and an inaccuracy of The precision of , (95% confidence interval) and the inaccuracy . The blood was analyzed immediately (within 10 min of sampling). It was injected into the analyzer from the blood-sampling syringe, with approx. 85 p L being required for each analysis. Three analyses were performed for each blood sample. These three individual values were recorded on the CRF and their mean was used in the evaluation. The baseline Metlib concentration was determined at 30, 15, and 0 minutes prior to Dental Gel 5% administration. The highest measured percentage of Metlib after application of the gel was identified (ChighMetHb) in each patient and the time of ChighMetHbWaS identified (thighMetHb). In case a peak of measured percentage of Metlib could be clearly identified in each patient, the peak would have been obtained directly from the Metlib levels as well as the time to reach the peak.

Statistical analysis and evaluation

The statistical analyses were performed at AstraZeneca R&D. All results were generated using the SAS® software version 6.12 system running on Windows NT 4.00. The pharmacokinetic and efficacy variables were summarized using standard descriptive statistics such as the mean, standard deviation, minimum and maximum values, and median. Adverse events were listed by patient. The difference in pocket depths before and after administration of Dental Gel 5% was derived. Missing data were to be assumed to be missing completely at random, causing a reduced sample size in analyses, tables, graphs, etc. when missing data occurred

Results

1. Demographics

Six male and five female 26- to 65-year-old Caucasians were included in the study. Seven of the patients were habitual smokers, three were previous smokers, one used snuff and one was a nonsmoker.

Patient demographics

Patient	Sex	Age	Weight (kg)	Height (cm)	Race	General appear.	General appear. Cavity
101	Male	61	99	182	Caucasian	Abnormal	Abnormal
102	Male	51	78	165	Caucasian	Normal	Normal
103	Female	65	92	168	Caucasian	Normal	Normal
105	Male	53	100	187	Caucasian	Normal	Normal
201	Male	49	78	185	Caucasian	Normal	Normal
202	Female	26	50	158	Caucasian	Normal	Normal
203	Female	58	77	175	Caucasian	Normal	Normal
204	Female	46	74	171	Caucasian	Normal	Normal
205	Male	38	76	165	Caucasian	Normal	Normal
206	Female	49	71	162	Caucasian	Normal	Normal
207	Male	54	92	186	Caucasian	Normal	Normal

(Data source: Appendix 16.2.4. Table 1.1.1.)

Age, weight, and height

Variable	MEAN	STD	MIN	MEDIAN	MAX
Age	50	11	26	51	65
Weight (kg)	81	14	50	78	100
Height (cm)	173	10	158	171	187

(Data source: Appendix 16.2.4. Table 1.1.2.)

2. Dose administration

All subjects received approx. 8.5 g of Dental 5% Gel. The application duration was similar for all subjects.

Dental Gel 5% administered per patient.

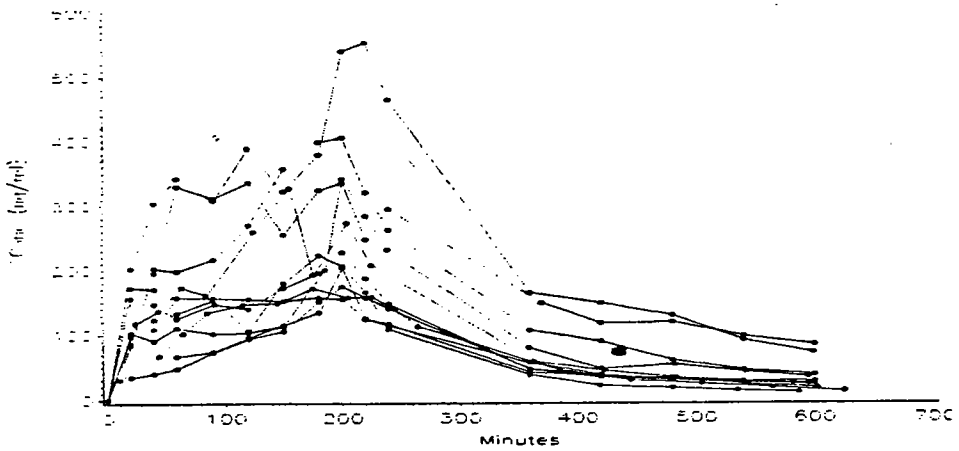
Centre	Patient	Amount of Dental Gel (g)	Dose Lidocaine (mg)	Dose Prilocaine (mg)	Duration of adm of Gel (min)
1	101	8.5	212.5	212.5	180
	102	8.6	215.0	215.0	154
	103	8.5	212.5	212.5	176
	105	8.6	215.0	215.0	162
2	201	8.7	217.5	217.5	201
	202	8.5	212.5	212.5	178
	203	8.0	200.0	200.0	180
	204	8.7	217.5	217.5	176
	205	8.6	215.0	215.0	178
	206	8.7	217.5	217.5	180
	207	8.7	217.5	217.5	180

(Data source: Appendix 16.2.4. Tables 1.7.1. and 1.7.4.)

3. Pharmacokinetic results and tabulations of individual patient data

A. Lidocaine

For lidocaine, Cmax ranged between 157 and 552 ng/mL and tmax between 120 and 220 min. The highest individual Cmax was reached 220 min after the start of application of the gel in Patient #206. In the other patients with the last cartridge applied immediately before completion at 3 hours, Cmax was 174 ng/mL (Pat #101), 204 ng/mL (Pat #204), and 342 ng/mL (Pat #207).



Lidocaine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine base, respectively) in periodontal pockets in 11 patients with widespread periodontal disease.

Cmax and tmax for Lidocaine, prilocaine, 2,6-xylidine, and o-toluidine following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine base, respectively) in periodontal pockets in 11 patients with widespread periodontal disease. Results are presented as mean + SD (min-max). tmax is presented as median (min-max).

	Cmax (ng/mL)	Cmax (nmol/L)	tmax* (min)
Lidocaine	283.8 ± 121.9 (157 – 552)	1211 ± 520 (671-2355)	200 (120-220)
Prilocaine	106.1 ± 44.7 (53 – 181)	482 ± 203 (242-823)	200 (120-200)
2,6-xylidine	18.0 ± 8.4 (8- 32)	148 ± 69 (68 - 260)	239 (175-240)
***0*-toluidine**	25.2 ± 10.9 (13-44)	235 ± 102 (120-411)	220 (90-240)

* from start of application of Dental Gel 5%

(Data source: Appendix 16.2.5. Tables 2.3.1., 2.3.3., 2.3.5., 2.3.7., 2.6.1., 2.6.3., 2.6.5., 2.6.7.)

In all but one of the patients five data-points were used for calculation of the terminal half-life of lidocaine. The terminal half-life ranged between 130 and 389 min. with mean value of 217.82 minutes.

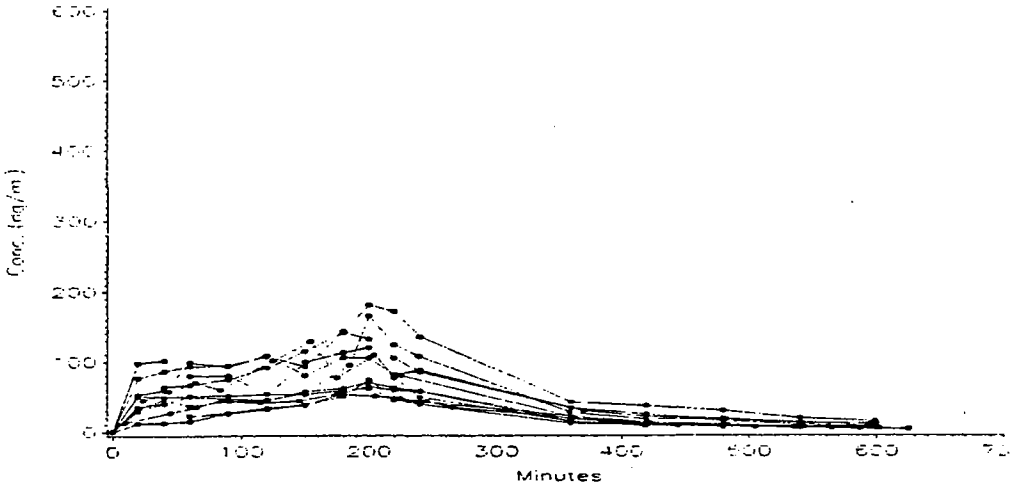
Pharmacokinetic parameters for lidocaine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	257.00	5.00	0.92	41445.00	49603.00	16.45
102	132.00	5.00	0.99	71688.00	74932.00	4.33
103	263.00	6.00	0.89	119775.00	151291.00	20.83
105	154.00	5.00	0.97	101480.00	109539.00	7.36
201	130.00	5.00	0.99	48461.00	50750.00	4.51
202	222.00	5.00	0.90	50658.00	57941.00	12.57
203	272.00	5.00	0.94	55227.00	64546.00	14.44
204	389.00	5.00	0.91	43103.00	57862.00	25.51
205	140.00	5.00	0.98	50627.00	52680.00	3.90
206	181.00	5.00	0.96	152190.00	171288.00	11.15
207	256.00	5.00	0.75	65858.00	78788.00	16.41
Mean	217.82	5.09	0.93	72773.82	83565.45	12.50
SD	79.91	0.30	0.07	36234.71	42328.73	7.11
Min	130.00	5.00	0.75	41445.00	49603.00	3.90
Max	389.00	6.00	0.99	152190.00	171288.00	25.51

(Data source: Appendix 16.2.5. Table 2.12.1.)

B. Prilocaine

For prilocaine, Cmax ranged between 53 and 181 ng/ml and tmax between 120 and 200 min. The highest individual Cmax was reached 200 minutes after the start of application of the gel in Patient #206. In the other patients with the last cartridge applied immediately before completion at 3 hours, Cmax was 64 ng/mL (Pat #101), 74 ng/mL (Pat #204), and 165 ng/mL (Pat #207).



Prilocaine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine base, respectively) in periodontal pockets in 11 patients with widespread periodontal disease.

In all individuals the last five data-points were used for calculation of the half-lives of prilocaine. The terminal half-life ranged between 118 and 343 min. with a mean value of 169.45 minutes.

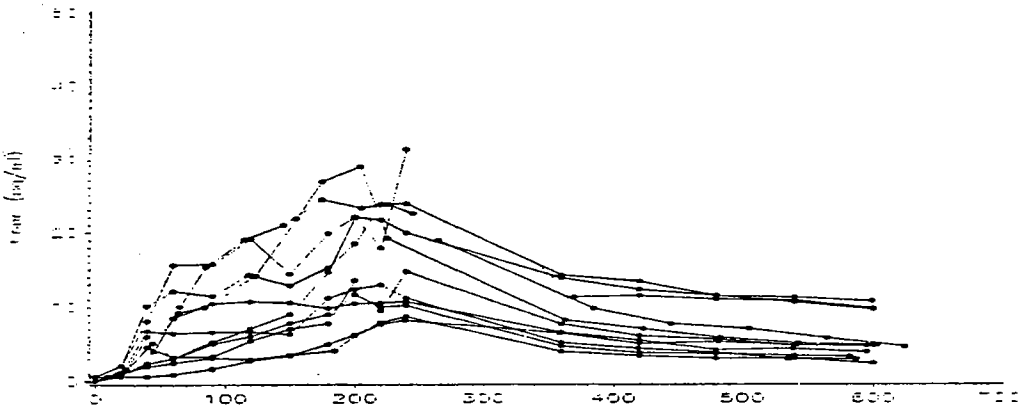
Pharmacokinetic parameters for prilocaine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	183.00	5.00	0.84	14297.00	15492.00	7.71
102	120.00	5.00	1.00	27008.00	27818.00	2.91
103	162.00	5.00	0.97	32063.00	34474.00	6.99
105	118.00	5.00	0.97	32350.00	33638.00	3.83
201	135.00	5.00	0.98	15052.00	15726.00	4.29
202	156.00	5.00	0.90	17889.00	19213.00	6.89
203	160.00	5.00	0.94	18235.00	19520.00	6.58
204	343.00	5.00	0.92	13991.00	17230.00	18.80
205	153.00	5.00	0.94	25804.00	26807.00	3.74
206	141.00	5.00	0.97	43803.00	46764.00	6.33
207	193.00	5.00	0.93	28527.00	31416.00	9.20
Mean	169.45	5.00	0.94	24456.27	26190.73	7.03
SD	62.08	0.00	0.04	9499.34	9874.82	4.36
Min	118.00	5.00	0.84	13991.00	15492.00	2.91
Max	343.00	5.00	1.00	43803.00	46764.00	18.80

(Data source: Appendix 16.2.5. Table 2.11.1.)

C. 2,6-xylidine

2,6-xylidine Cmax ranged between 68 and 260 nmol/L and tmax was reached 175-240 min after the start of application. The terminal half-life, calculated on the last five data-points, ranged between 226 and 1069 min. The ratio AUCinf 2,6-xylidine/AUCinf lidocaine ranged between 0.07 and 0.18 and the ratio Cmax2,6-xylidine/Cmax lidocaine was 0.05-0.27.



2,6-xylidine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine base respectively) in periodontal pockets in 11 patients with widespread periodontal disease.

Pharmacokinetic parameters for 2,6-xylidine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	350.00	5.00	0.89	2257.10	3484.45	35.22
102	310.73	5.00	0.94	6627.84	8702.30	23.84
103	1069.06	5.00	0.73	9001.98	24576.22	63.37
105	481.12	5.00	0.99	7024.08	13770.89	48.99
201	225.60	5.00	0.98	7722.62	9245.95	16.48
202	357.17	5.00	0.74	4168.94	6105.63	31.72
203	506.98	5.00	0.84	3237.49	5584.22	42.02
204	380.22	5.00	0.83	4156.60	6648.37	37.48
205	261.25	5.00	0.90	3654.53	4700.45	22.25
206	590.25	5.00	0.87	8384.35	17403.01	51.82
207	696.27	5.00	0.54	2945.87	7578.42	61.13
Mean	475.33	5.00	0.84	5380.13	9799.99	39.48
SD	242.81	0.00	0.13	2410.42	6368.70	15.63
Min	225.60	5.00	0.54	2257.10	3484.45	16.48
Max	1069.06	5.00	0.99	9001.98	24576.22	63.37

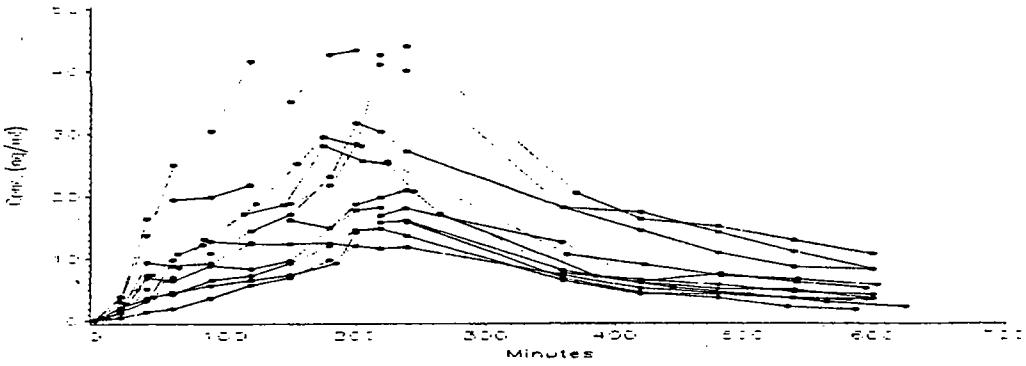
(Data source: Appendix 16.2.5. Table 2.13.1.)

Ratio AUCinf 2,6-xylidine/AUCinf lidocaine and ratio Cmax 2,6-xylidine/Cmax lidocaine

Variable	MEAN	STD	MIN	MEDIAN	MAX
AUCinf 2.6-xylidine/AUCinf Lidocaine	0.11	0.03	0.07	0.11	0.18
Cmax 2.6-xylidine/Cmax Lidocaine	0.13	0.06	0.05	0.11	0.27

D. o-toluidine

o-toluidine Cmax ranged between 120 and 411 nmol/L and tmax was reached 90-240 min after the start of application. The terminal half-life, calculated on the five last data-points ranged between 121 - 338 min. The ratio AUCinf o-toluidine/AUCinf prilocaine ranged between 0.19 and 0.56 and Cmax o-toluidine/Cmax prilocaine ranged between 0.23 and 1.08.



o-toluidine plasma concentrations following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine base, respectively) in periodontal pockets in 11 patients with widespread periodontal disease.

Pharmacokinetic parameters for *o*-toluidine

Patient	t1/2 (min)	No. obs	Rsq (adj)	AUCt (ng*min/ml)	AUCinf (ng*min/mL)	Residual area (%)
101	231.00	5.00	0.92	4341.83	5598.06	22.44
102	291.00	5.00	0.96	8187.71	10618.75	22.89
103	268.00	5.00	0.97	15022.55	19248.22	21.95
105	219.00	5.00	0.89	9250.16	11719.37	21.07
201	147.00	5.00	1.00	6788.66	7286.02	6.83
202	260.00	5.00	0.87	4653.06	5924.37	21.46
203	313.00	5.00	0.79	4197.10	5717.77	26.60
204	273.00	5.00	0.97	6063.70	7729.01	21.53
205	121.00	5.00	0.97	4658.77	4973.06	6.32
206	192.00	5.00	0.95	11940.70	14347.63	16.78
207	338.00	5.00	0.43	5411.76	8051.14	32.78
Mean	241.36	5.00	0.88	7319.64	9201.22	20.06
SD	67.50	0.00	0.16	3513.93	4434.73	7.76
Min	121.00	5.00	0.43	4197.10	4973.06	6.32
Max	338.00	5.00	1.00	15022.55	19248.22	32.78

(Data source: Appendix 16.2.5. Table 2.14.1.)

Ratio AUCinf o-toluidine / AUCinf prilocaine and ratio Cmax o-toluidine / Cmax prilocaine

Variable	MEAN	STD	MIN	MEDIAN	MAX
AUCinf o-toluidine/AUCinf Prilocaine	0.36	0.10	0.19	0.35	0.56
Cmax o-toluidine/Cmax Prilocaine	0.53	0.24	0.23	0.47	1.08

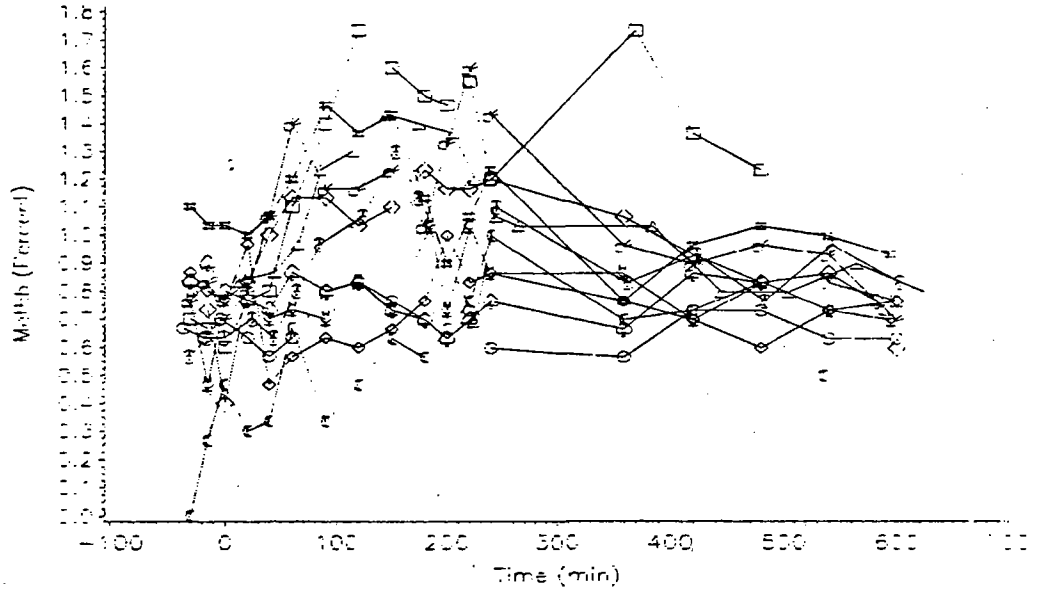
(Data source: Appendix 16.2.5. Table 2.8.5. and 2.15..2)

Pharmacokinetic conclusion

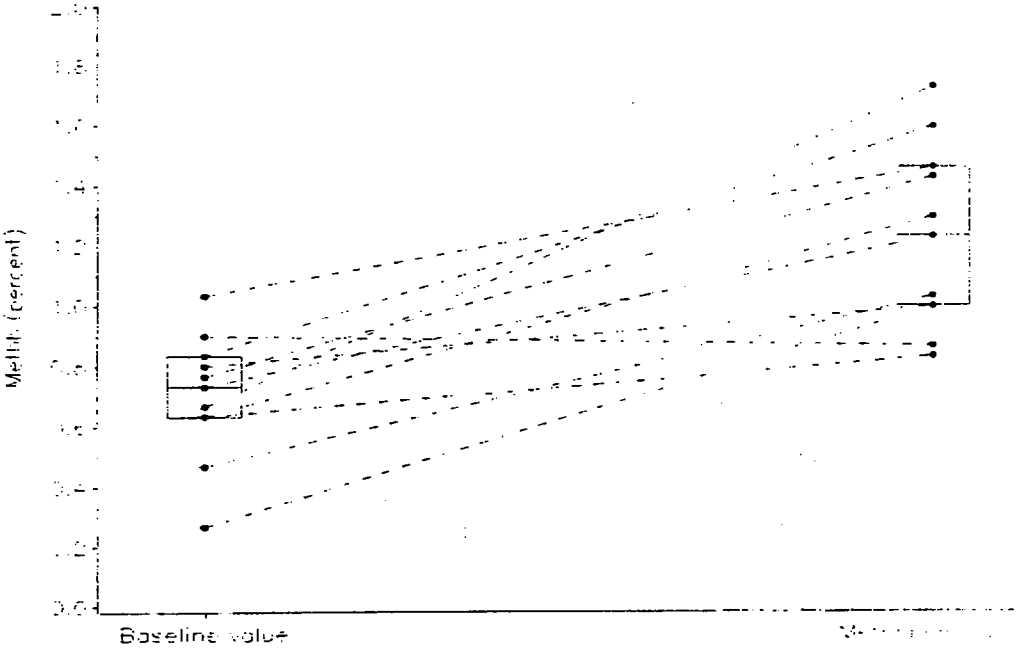
Following application of 8.0-8.7 g Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine respectively) for 154-201 minutes to all periodontal pockets in patients with widespread periodontal disease undergoing probing and SRP, peak plasma concentrations of lidocaine and prilocaine (mean ± sd (min-max)) were 284 ± 122 (157-552) ng/ml and 106 ± 45 (53-181) ng/mL, occurring 120-220 and 120-200 minutes, respectively, after the start of application of the gel. These levels are well below threshold levels for initial signs of CNS toxicity (5000-6000 ng/mL). The systemic exposure of 2,6-xylidine and o-toluidine was low in comparison to their parent compounds, with individual AUCinf-ratios of 0.07-0.18 and 0.19-0.56 respectively.

4. Safety - Clinical laboratory evaluation

Immediately before the start of application, Metlib levels were within the range 0.0-1.1%. After application of the gel there was a slight increase in Metlib levels. The highest measured individual values (ChighMetUb), 0.83-1.73%, were reached 60-240 min. after the start of application of the gel. All levels were below 2% and thus within reference levels (< 2 %).



Metlib (%) following application of 8.0-8.7 g of Dental Gel 5 % (200.0-217.5 mg of lidocaine and prilocaine, respectively) in periodontal pockets in 11 patients with widespread periodontal disease.



Baseline Metlib (%) and ChighMetHb(%), scatter and boxplot.

thighMetHb(min) and ChighMetHb(%) following application of 8.0-8.7 g of Dental Gel 5% (200.0-217.5 mg of lidocaine and prilocaine, respectively) in periodontal pockets in 11 patients with widespread periodontal disease.

Variable	MEAN	STD	MIN	MEDIAN	MAX
$thigh_{MetHb}$	155.8	55.49	60.00	154.0	240.0
$Chigh_{MetHb}$	1.23	0.30	0.83	1.23	1.73

(Data source: Appendix 16.2.5. Table 2.10.9.)

The Applicant stated that the majority of adverse events were transient and none were of major clinical significance. Methemoglobin remained within reference levels (<2%).

DISCUSSION AND OVERALL CONCLUSIONS

The highest individual peak plasma concentrations for lidocaine and prilocaine were 552 ng/mL and 181 ng/mL, respectively.

As the toxicity of lidocaine and prilocaine are additive, the safety evaluation should be based on the sum of these substances.

The mean terminal half-lives of lidocaine and prilocaine, 3.6 and 2.8 hours, respectively, were longer than reported following intravenous administration, 1.6 hours for both substances which reflects their absorption from the periodontium.

The peak plasma levels of lidocaine and prilocaine were reached within 40 min after completion of the Dental Gel 5% application.

The plasma levels of lidocaine obtained in the present study appear to be lower than those following intra-oral injections of Xylocaine 2% with epinephrine. An intra-oral injection of 200 mg lidocaine HC1 produces peak plasma levels of about 2000 ng/mL.

The plasma levels of lidocaine and prilocaine were similar to those obtained following application of 10g EMLA® cream to leg ulcers (peak plasma levels of 5-840 ng/mL and 20-80 ng/mL for lidocaine and prilocaine respectively)

The systemic exposure of 2,6-xylidine and o-toluidine was low in comparison to their parent compounds. The individual ratio of AUCinf 2,6-xylidine/AUCinf lidocaine was 0.07-0.18 and of AUCinf o-toluidine /AUCinf prilocaine 0.19-0.56. These ratios are in accordance with findings following application of repeated doses of EMLA® cream to leg ulcers and following application of 0.9-3.5 g of Dental Gel 5% to periodontal pockets. This indicates that the relative extent of metabolism of lidocaine to 2,6-xylidine and prilocaine to o-toluidine, respectively, was similar following application to periodontal pockets and leg ulcers.

With respect to safety, methemoglobin levels remained within reference limits (<2%) and were well below levels associated with clinical symptoms (20%) and levels requiring treatment (30%).

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/s/

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