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Plasma levels of lidocaine and prilocaine after application of Oraqix®, a new intrapocket anesthetic, in patients with advanced periodontitis

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Abstract

Background, aims: Oraqix®, a new non-injection local anesthetic, lidocaine/prilocaine gel 5%, has been developed to provide pain relief in association with periodontal probing and scaling/root planing (SRP). The aim of this open study was to describe the plasma profiles of lidocaine and prilocaine following a single dose of Oraqix® to patients with advanced periodontitis.

Methods: 10 patients with 18 to 28 teeth with pocket depths of at least 4 mm were included. Oraqix® was applied in the pockets around all the teeth in the mouth by means of a blunt applicator. The total dose applied per patient was 0.9 to 3.5 g. Directly thereafter all the pockets were probed and 3 teeth subjected to SRP. The mouth was rinsed out with a glass of water 20–27 min after the application of the gel. Blood samples were collected before and up to 90 min after the start of application of Oraqix®.

Results: Peak plasma concentrations of lidocaine (99–266 ng/ml) and prilocaine (46–118 ng/ml) occurred 20–40 min after the start of application. These levels were low compared to those reported to cause initial signs of CNS toxicity (5000–6000 ng/ml). Side-effects were few and mild local effects of short duration.

Discussion: In conclusion, there is a large safety margin with respect to systemic effects following the application of up to 3.5 g Oraqix® in periodontal pockets.

Key words: anesthetics, local; periodontal diseases; mouth mucosa; lidocaine; prilocaine; pharmacokinetics

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Oraqix®, AstraZeneca, a new intrapocket anesthetic, has been shown to provide efficient pain control during SRP (Friskopp et al. 2001). Oraqix® contains the local anesthetics lidocaine and prilocaine (25 mg/g of each substance) and a thermosetting agent. The formulation is fluid at room temperature but increases in viscosity when applied into the periodontal pocket, thereby enabling the gel to remain in place for the time necessary to induce local anesthesia.

The main objective of this open study was to determine the plasma levels of lidocaine, prilocaine, and two of their metabolites following a single dose of Oraqix® to patients with severe periodontal disease requiring SRP.

Material and Methods

Oraqix® was applied in the pockets around all the teeth. Directly thereafter all the pockets were probed, 3 teeth were subjected to SRP, and the mouth was then rinsed out with a glass of water. Blood samples were collected during the study procedure.

Patients

Following Ethics Committee approval and written informed consent, ten patients with severe periodontal disease scheduled for SRP were recruited from a specialist periodontal clinic in Sweden. The periodontal pockets had to be deep and widespread, with at least 16 teeth with pocket depths of 4 mm or more. The patients were healthy apart from periodontitis and had a normal general appearance of the oral cavity. During the week before and during the study period, administration of an am-

ide local anesthetic other than Oraqix® was not allowed.

Procedures

Oraqix® was applied directly in the periodontal pockets using a 23-G blunt applicator. The pockets were filled up to the gingival margin. The dose of Oraqix® was assessed by weighing the syringe before and after application of the gel. In order to maximize the rate of absorption, Oraqix® was applied as rapidly as possible and in order to maximize the extent of absorption, the gel remained within the pockets for as long as possible, i.e., during the time of probing and SRP, before the mouth was rinsed out with a glass of water. Probing of the periodontal pockets was performed on all teeth using a standard periodontal probe, after which SRP was performed on three teeth using a manual scaler. A visual inspection of the shape, pattern, and color of the gingival mucosa was performed before and after the application of Oraqix® but before probing. Information about side effects was collected from before application of the gel until a follow-up telephone call 24–48 h after the study period.

Blood sampling

An intravenous catheter was inserted on the volar side of the right arm before the start of the Oraqix® application. 5 ml of blood was collected in heparinized tubes before and 10, 20, 30, 40, 60, 75, and 90 min after the start of application of Oraqix®. The blood was centrifuged within 60 min of collection. The plasma was transferred to polypropylene tubes and the plasma samples were stored at −20°C until assayed. Plasma concentrations of lidocaine and prilocaine were determined as well as the lidocaine metabolite 2,6-xylidine and the prilocaine metabolite *o*-toluidine.

Bioassay

Quantification of lidocaine and prilocaine in plasma

The concentration of lidocaine and prilocaine in plasma was determined by gradient liquid chromatography and mass spectrometry with electrospray ionization and selected ion monitoring. The limit of quantification was set at 1 ng/ml for lidocaine and prilocaine. The between-day coefficients of variation (CV) for lidocaine and prilocaine were less than 10% at concentrations of 4–190 ng/ml and the accuracy was 93–99%.

Quantification of 2,6-xylidine and o-*toluidine in plasma*

The concentration of 2,6-xylidine and *o*-toluidine in plasma was determined by coupled-column, reversed-phase, liquid chromatography using mass spectrometry and electrospray ionization and selected ion monitoring. The limit of quantification was 0.6 ng/ml for 2,6-xylidine and 1 ng/ml for *o*-toluidine. The between-days CV was less than 11% at concentration levels of 1.2–9.2 ng/ml of 2,6-xylidine and less than 8% at concentration levels of 2.2–17.8 ng/l of *o*-toluidine. The accuracy was in the range 95–109% for both compounds.

Pharmacokinetic evaluation

The pharmacokinetic evaluation was performed according to non-compartmental analysis. The peak plasma level (C_{max}) and the time to reach C_{max} (t_{max}) were obtained directly from the observed plasma concentrations. The ratio of C_{max} for 2,6-xylidine and lidocaine and the ratio of C_{max} for *o*-toluidine and prilocaine were calculated based on molar concentrations of the substances. The molecular weight used in the calculations for lidocaine, prilocaine, 2,6-xylidine, and *o*-toluidine were 234.34, 220.31, 121.18, and 107.16, respectively.

Statistical methods

The dose proportionality in C_{max} was evaluated with a power model (Gough et al. 1985). The general linear model $\ln(C_{maxi})=\alpha+\beta\ln(\text{dose}_i)+\varepsilon_i$, where α is the intercept, β is the regression slope, and ε_i is a random error, was applied. Rewritten as $C_{maxi}=\alpha'\text{dose}_i^{\beta}\varepsilon'_i$, where $\alpha'=e^{\alpha}$ and $\varepsilon'_i=e^{\varepsilon}$, 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}.

Table 1. Dose of Oraqix®, pocket depth probing and scaling timelines

Pat no.	No. teeth with pockets <4 mm	No. teeth with pockets ≥4 mm	No. teeth with pockets 4–7 mm	No. teeth with pockets ≥8 mm	Total dose (g)	Duration of application (min)	Duration of probing*	Duration of SRP (min)	Time from start of application to rinsing (min)
101	0	28	20	8	1.8	7	10	9	26
102	0	26	22	4	2.0	7	14	4	25
103	0	18	18	0	0.9	7	8	7	22
104	5	23	20	3	1.4	7	8	5	20
105	6	24	22	2	1.4	7	8	6	21
106	0	25	19	6	2.0	7	10	7	24
108	3	25	18	7	1.7	6	9	5	20
109	0	26	14	12	3.5	9	10	8	27
110	0	24	19	5	3.0	7	7	9	23
111	4	21	16	5	2.6	8	10	8	26
mean	1.8	24	18.8	5.2	2.0	7	9.6	6.3	23
SD	2.5	3	2.5	3.4	0.8	1	2.0	2.4	2.8
median	0	24	19	5	1.8	7	9.5	7	23
min	0	18	14	0	0.9	6	7	4	20
max	6	28	22	12	3.5	9	14	9	27

* Probing time was calculated as: Time from end of administration of Oraqix® until start of SRP.

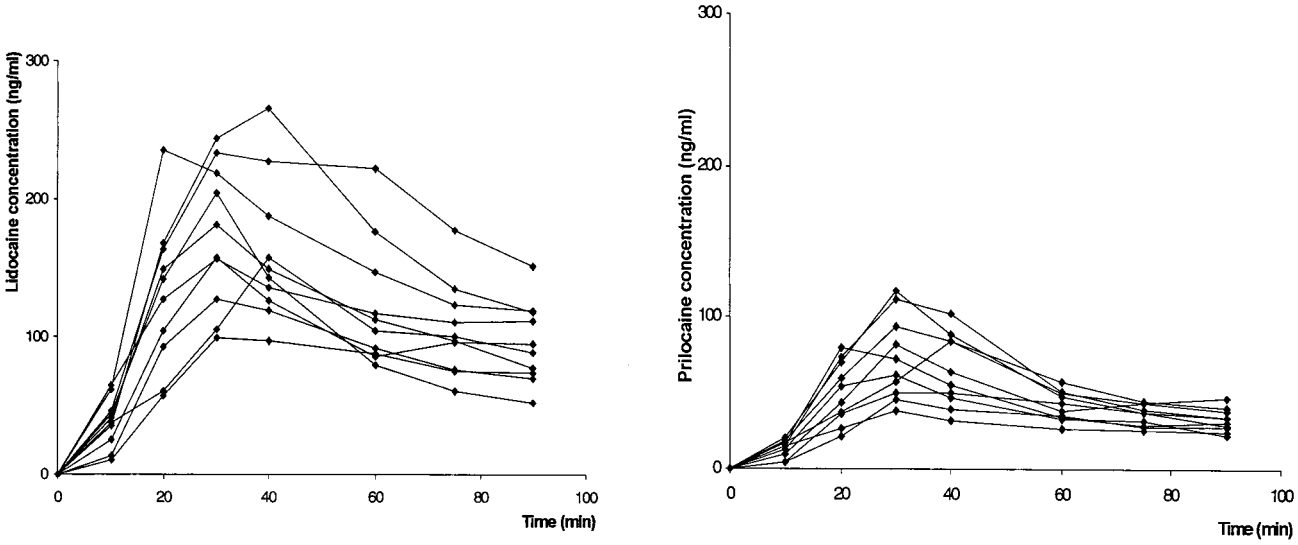

Fig. 1. Lidocaine and prilocaine plasma concentration time profiles following application of 0.9–3.5 g Oraqix® in periodontal pockets in 10 patients with severe and widespread periodontal disease.

Results

Three male and 7 female patients aged 38 to 56 years were included in the study. The total dose of Oraqix® applied per patient was 0.9–3.5 g. The timelines for each study procedure are shown in Table 1. SRP was not interrupted due to pain in any of the patients.

Lidocaine and prilocaine plasma levels

The absorption of lidocaine and prilocaine from Oraqix® was rapid, with peak plasma concentrations occurring 20–40 and 30–40 min, respectively, after the start of application of Oraqix®. The lidocaine C_{max} was in the range 99–266 ng/ml and the prilocaine C_{max} was in the range 46–118 ng/ml (Table 2, Fig. 1).

In the linear regression used to examine the dose proportionality in C_{max}, about 40% and 53% of the variance in C_{max} for lidocaine and prilocaine, respectively, could be explained by the dose given. C_{max} values were estimated to increase by a factor of 1.48 (90% confidence interval 1.14–1.82) and 1.61 (90% confidence interval 1.24–2.09) for lidocaine and prilocaine, respectively, when doubling the dose of Oraqix®.

The lidocaine metabolite 2,6-xylidine and the prilocaine metabolite *o*-toluidine

The C_{max} and t_{max} of 2,6-xylidine and *o*-toluidine could not be adequately identified in one of the patients due to inadequate plasma volumes in some samples collected for metabolite determination. In another patient the C_{max} and t_{max} of *o*-toluidine could not be adequately identified due to too short

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

	Lidocaine		Prilocaine		2,6 xylidine			*o*-toluidine		
Pat no.	C_{max} (ng/ml)	t_{max} (min)	C_{max} (ng/ml)	t_{max} (min)	C_{max} (ng/ml)	t_{max} (min)	C_{max} ratio[a)]	C_{max} (ng/ml)	t_{max} (min)	C_{max} ratio[b)]
101	157	40	84	40	4.4	75	0.05	9.7[c)]	90[c]	0.24
102	157	30	82	30	2.2	60	0.03	5.2	60	0.13
103	127	30	50	30, 40	5.5[d]	60[d]	0.08	5.7[d)]	90[d]	0.23
104	99	30	46	30	5.9	60	0.12	7.3	75	0.33
105	236	20	72	30	5.2	75	0.04	9.0	75	0.26
106	181	30	62	30	14.2	75	0.15	14.4	75	0.48
108	156	30	39	30	4.1	75	0.05	7.4	60	0.39
109	204	30	118	30	5.7	75	0.05	6.9	60	0.12
110	234	30	94	30	8.4	60	0.07	15.6	60	0.34
111	266	40	112	30	1.6	75	0.01	6.4	60	0.12
X	171.7		75.9		5.7		0.07	8.8		0.26
SD	50.7		27.2		3.5		0.04	3.6		0.12
median	169	30	77	30	5.3	75	0.05	7.3	67.5	0.25
min	99	20	46	30	1.6	60	0.01	5.2	60	0.12
max	266	40	118	40	14.2	75	0.15	15.6	90	0.48

[a)] The molar C_{max} ratio of 2,6 xylidine/lidocaine
[b)] The molar C_{max} ratio of *o*-toluidine/prilocaine
[c)] C_{max} and t_{max} are approximations since the sampling times were too short to identify C_{max} and t_{max}.
[d)] C_{max} and t_{max} are approximations since the plasma volumes were too small to determine 2,6 xylidine and *o*-toluidine in all samples collected.

period of blood sampling. The values obtained for C_{max} and t_{max} were, however, considered to be reasonable approximations since the plasma levels of 2,6-xylidine and *o*-toluidine were rather flat in the latter part of the plasma curve (Table 2). T_{max} was reached 60–75 min and 60–90 min after the start of application of Oraqix® for 2,6-xylidine and *o*-toluidine, respectively. The C_{max} was 1.6–14.2 ng/ml for 2,6-xylidine and 5.2–15.6 ng/ml for *o*-toluidine. The ratio of C_{max} 2,6-xylidine/ C_{max} lidocaine was in the range 0.01–0.15 and the ratio of C_{max} *o*-toluidine / C_{max} prilocaine was between 0.12 and 0.48 (Table 2).

Side effects

Side effects reported ($n=5$) were mild local effects of short duration, i.e., a bad taste from the gel ($n=1$), anesthesia of the throat or tongue due to overflow of the gel ($n=2$), and minor discomfort during application of the gel ($n=2$). No signs of systemic toxicity or mucosal irritation were seen.

Discussion

The present study was designed to document the systemic safety of Oraqix® and it was provocative with respect to factors expected to affect the absorption of lidocaine and prilocaine from the gel.

In this open study with plasma sampling throughout the SRP and probing procedures, it was not possible to assess the efficacy of Oraqix®. However, the overall impression in all patients was that Oraqix® was satisfactory for the SRP and probing procedures since they were not interrupted due to pain in any of the patients. Oraqix® has been shown to provide efficient pain control during SRP in a previous study (Friskopp et al. 2001).

The doses of Oraqix® used in the present study ranged from 0.9 to 3.5 g, which corresponds to 22.5–87.5 mg of lidocaine and prilocaine, respectively. In order to maximize the rate of absorption, Oraqix® was applied as rapidly as possible (over 6–9 min) and also in order to maximize the extent of absorption, the gel remained within the pockets for as long as possible, i.e., during the time of probing and SRP, before the mouth was rinsed out with a glass of water, 20–27 min after the start of application of the gel.

The absorption of lidocaine and prilocaine was rapid in all patients. Peak plasma concentrations of both anesthetics were reached within 40 min after the application of Oraqix® had started. The individual highest C_{max} values were 266 ng/ml for lidocaine and 118 ng/ml for prilocaine. In general, the plasma levels of prilocaine were lower than those of lidocaine. This is in accordance with the larger volume of distribution and higher clearance for prilocaine compared to lidocaine (Tucker 1986). The obtained lidocaine levels were considerably lower than those following perioral injections of xylocaine 2% with epinephrine. A perioral injection of 200 mg lidocaine produces C_{max} values of about 2000 ng/ml (Cannell et al. 1975, Eichbohm et al. 1991). Considering that the Oraqix® doses used in the present study contained 11–44% of the lidocaine dose administered as a perioral injection, the peak plasma levels of lidocaine from Oraqix® appear to be somewhat lower than the peak plasma levels following injection. This is to be expected since the rate of absorption from the periodontal pockets is likely to be slower than from perioral injection. The extent of absorption is also expected to be lower with Oraqix® than with a perioral injection due to incomplete absorption of Oraqix®. Following application of Oraqix®, some gel is rinsed out from the periodontal pockets and the oral cavity and minor amounts of the gel may be swallowed during the procedure.

The absorption of lidocaine and prilocaine from EMLA® cream, containing lidocaine and prilocaine in the same concentration as in Oraqix®, into the systemic circulation has been documented for gingival mucosae (Pere et al. 1992, Haasio et al. 1990). The application of 4 g EMLA® cream for 4 min to the gingival mucosa in 25 patients resulted in maximum individual C_{max} values of 470 ng/ml (5 min after application) and 210 ng/ml (10 min after application) for lidocaine and prilocaine, respectively (Pere et al. 1992, Haasio et al. 1990). This suggests that higher C_{max} values can be expected following application of Oraqix® in the periodontal pockets than from EMLA® cream to the gingival mucosa.

The lack of systemic effects in the present study is in accordance with the findings for the plasma levels of lidocaine and prilocaine. Assuming that the toxicity of lidocaine and prilocaine are additive, the safety evaluation should be based on the sum of these substances. Consequently, in the present study the plasma levels of lidocaine and prilocaine following the application of Oraqix® to patients with severe periodontitis indicate an at least tenfold safety margin in comparison to initial signs of CNS toxicity expected to appear at 5000–6000 ng/ml (Tucker & Mather 1998).

Since the pharmacokinetic information on the metabolites 2,6-xylidine and *o*-toluidine are scarce these metabolites were determined in the present study with a more sensitive method than previously used. The peak plasma levels of the metabolites 2,6-xylidine and *o*-toluidine were considerably lower and were reached later than for the parent compounds lidocaine and prilocaine, respectively. The peak plasma levels of 2,6-xylidine and *o*-toluidine were 1–15% and 12–48% of the peak plasma levels of lidocaine and prilocaine, respectively. These findings were in accordance with a previous study on EMLA® applied to leg ulcers (Lok et al. 1999).

In conclusion, Oraqix® is safe following application of a total dose of 0.9–3.5 g Oraqix® in the periodontal pockets. The peak plasma concentrations of lidocaine and prilocaine were well below those reported to cause initial signs of CNS toxicity.

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Zusammenfassung

Plasmatiter von Lidocain und Prilocain nach Applikation von Oraqix®, ein neues Anästhetikum für die Anwendung in den Taschen von Patienten mit fortgeschrittener Parodontitis

Oraqix®, ein neues Lokalanästhetikum, welches nicht injiziert wird, ein 5%iges Lidocain/Prilocain-Gel, wurde entwickelt, um bei der parodontalen Sondierung und bei Scaling/Wurzelglättung (SRP) eine Schmerzlinderung zu ermöglichen. Das Ziel dieser offenen Studie war es, bei Patienten mit fortgeschrittener Parodontitis die Plasmaprofile von Lidocain und Prilocain nach Applikation einer Einzeldosis von Oraqix® zu beschreiben. Es wurden 10 Patienten mit 18 bis 28 Zähnen und Taschentiefen von wenigstens 4 mm in die Studie aufgenommen. In die Taschen von

allen Zähnen im Mund wurde Oraqix® mittels eines stumpfen Applikators eingebracht. Die Gesamtdosis, die pro Patient appliziert wurde betrug zwischen 0.9 und 3.5 g. Direkt nach Applikation wurden alle Taschen sondiert und bei 3 Zähnen wurde ein SRP durchgeführt. 20–27 Min. nach der Gel-Applikation wurde der Mund mit einem Glas Wasser ausgespült. Vor und bis zu 90 Min. nach dem Start der Applikation wurden Blutproben entnommen. Die Höchstwerte der Plasmakonzentration von Lidocain (99–266 ng/ml) und Prilocain (46–118 ng/ml) waren 20–40 Min. nach dem Beginn der Applikation vorhanden. Im Vergleich mit den Titern, von denen über initiale Anzeichen einer CNS-Toxizität berichtet wird (5000–6000 ng/ml), sind diese niedrig. Es gab wenige Nebenwirkungen und leichte lokale Effekte waren von kurzer Dauer.

Résumé

Taux plasmatiques de lidocaine et de prilocaine après application d'Oraqix®, un nouvel anesthésique intra poche, chez des patients atteints de parodontites avancées

Oraqix®, un nouvel anesthésique local non injectable, gel à 5% de lidocaine/prilocaine, a été développé pour entrainer un soulagement de la douleur lors du sondage parodontal et du détartrage/surfaçage radiculaire (SRP). Le but de cette étude ouverte était de décrire les profils plasmatiques de lidocaine et de prilocaine consécutifs à une dose unique d'Oraqix® chez des patients atteints de parodontites avancées. 10 patients ayant 18 à 28 dents présentant des poches d'une profondeur d'au moins 4 mm furent inclus. Oraqix® était appliqué dans les poches autour de toutes les dents de la bouche à l'aide d'un applicateur émoussé. La dose totale appliqué par patient était 0.9 à 3.5 g. Juste après, toutes les dents furent sondées et 3 dents furent soumises au SRP. La bouche était rinçée avec un verre d'eau 20–27 min après l'application du gel. Des échantillons sanguins furent prélevés avant et jusqu'à 90 min après le ðéut de l'application d'Oraqix®. Le pic des concentrations plasmatiques de lidocaine (99–266 ng/ml) et de prilocaine (46–118 ng/ml) apparaissaient 20–40 min après le début de l'application. Ces niveaux étaient bas comparés à ceux rapportés comme responsables des signes initiaux de toxicité CNS (5000–6000 ng/ml). Les effets secondaires étaient minimes et les effets locaux bénins et de courte durée.

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