Plasma levels of lidocaine, *o*-toluidine, and prilocaine after application of 8.5 g Oraqix® in patients with generalized periodontitis: effect on blood methemoglobin and tolerability

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Oraqix®, a novel non-injectable anesthetic gel containing lidocaine and prilocaine and a thermosetting agent has been developed to provide localized anesthesia in periodontal pockets during scaling/root planing (SRP). The aim of this open study was to determine the plasma levels of lidocaine and prilocaine following application of 8.5 g Oraqix (5 cartridges) to 11 patients with generalized periodontitis (≥49% of tooth pockets ≥5 mm and ≥23% of pockets ≥6 mm). Oraqix was applied to the pockets during periodontal probing and SRP over a 2.6–3.4 h period. Blood samples were collected up to 10 h after the start of application of Oraqix. Peak plasma levels of lidocaine (0.16–0.55 mg/L) and prilocaine (0.05–0.18 mg/L) occurred 2.0–3.7 h and 2.0–3.3 h, respectively, after the start of application of Oraqix. These levels are well below threshold levels for initial signs of central nervous system (CNS) toxicity. In conclusion, application of 8.5 g Oraqix (212.5 mg of lidocaine base and 212.5 mg of prilocaine base) in periodontal pockets was well tolerated and displayed a wide safety margin with respect to plasma levels normally associated with systemic toxicity. □ *Lidocaine; local anesthetics; periodontal disease; pharmacokinetics; prilocaine*

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Oraqix®, AstraZeneca, a novel non-injectable anesthetic gel, has been developed to provide localized anesthesia in periodontal pockets in conjunction with periodontal scaling/root planing (SRP). Oraqix contains the local anesthetics lidocaine and prilocaine in the same concentration as in EMLA® cream (25 mg base/g gel of each substance), and a thermosetting agent. The unique nature of Oraqix is its ability to remain fluid at room temperature and to increase in viscosity when introduced into the periodontal pocket. This enables Oraqix to be introduced into the periodontal pocket in a fluid state by means of a blunt applicator and then remain in the pocket for the time necessary to induce local anesthesia. Oraqix has been shown to provide efficient pain control during SRP in 3 placebo-controlled studies (1–3). In these studies, on average 1 cartridge of Oraqix (1.7 g) was used for SRP of 1 quadrant of the dentition. The main objective of this open study was to determine the plasma levels of lidocaine, prilocaine, *o*-toluidine (prilocaine metabolite), and methemoglobin blood (metHb) levels in order to evaluate the potential for systemic toxicity of 5 cartridges of Oraqix (8.5 g) during pocket depth probing and SRP in patients with generalized periodontal disease. The study was an experimental setting intended to maximize exposure. The drug treatment (drug dose, duration of application, and number of teeth treated simultaneously) was beyond what can be expected in most periodontal patients.

MetHb levels were determined, since *o*-toluidine has the potential to cause methemoglobinemia at high doses of prilocaine, i.e. parenteral doses above 600 mg prilocaine (4). Local tolerability of Oraqix was also assessed.

Materials and methods

Eleven patients with generalized chronic periodontitis scheduled for SRP participated in the study. They were recruited from a Specialist Dental Clinic and the Institute of Odontology, Karolinska Institutet. All patients were given verbal and written information and signed an informed consent before any study-related procedures were undertaken. The study was approved by the ethics committee of Karolinska Institutet, Huddinge University Hospital and was conducted in accordance with the Declaration of Helsinki and European Union guidelines for good clinical practice.

Patients had to have a minimum of 20 natural teeth to be included in the study. At least 50% of the pockets had to be ≥5 mm and 30% ≥6 mm assessed by probing the pocket depth at 4 sites on each tooth in the 4 weeks before the study day. Pocket depths were measured using a periodontal probe (Hu-Friedy Inc. Chicago, Ill., USA). During the week before and during the study day, administration of local anesthetics other than Oraqix was not allowed.

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Any other medication considered necessary for the patient's welfare, e.g. for pain related to the SRP, could be given, however.

On the study day, 5 cartridges of Oraqix were administered to each patient by means of a standard 1.8-mL dental cartridge system with a blunt 23-G applicator. First, the gel was applied at the gingival margin around all the teeth of the mouth. Immediately after, Oraqix was applied to the periodontal pockets of all the teeth followed by probing to assess the periodontal pocket depths and bleeding on probing. Bleeding from the gingival sulcus was scored 1, while absence of bleeding was scored 0 (5). Thereafter the gel was applied to the periodontal pockets of 2 teeth. This was followed by SRP of these teeth using hand instruments. Reapplication of the gel was allowed in the case of pain from SRP. If the SRP was still painful after reapplication, the procedure was interrupted for the tooth in question, but was then continued on the next tooth. The interrupted teeth were treated at an appointment outside the study. The application of gel and subsequent SRP of another two teeth at the time was repeated in a consecutive fashion until all 5 cartridges had been administered or up to 3 h after the start of application of Oraqix, whichever occurred first. If some of the predetermined dose still remained at 3 h after the start of application of the gel, the remaining gel was applied to the previously treated pockets. The exact dose administered was assessed by weighing the cartridges and syringes before and after the application of Oraqix.

During the procedures, excess saliva was removed by suction when required. Expectoration was allowed, although the patient was not allowed to rinse his/her mouth with water until 30 min after the application of Oraqix was completed. In the event of an uncomfortable dry mouth, the mucous membranes were sprayed with water.

A visual inspection of the oral cavity was performed before the start of application of the gel, immediately before the start of the probing procedure, before leaving the clinic, and 1 week thereafter at a follow-up visit. Information about adverse events was collected from immediately before application of the gel until the follow-up visit.

Blood sampling

Peripheral venous blood samples were collected from an indwelling catheter 30 and 15 min before and immediately prior to gel application, and thereafter 20, 40, 60, 90, 120, 150, 180, 200, 220, and 240 min and 6, 7, 8, 9, and 10 h after the start of application of Oraqix.

Blood samples for determination of metHb were taken at all time-points in special heparinized syringes (PICO, Radiometer, Copenhagen) and analysed within 10 min of sampling.

Samples for pharmacokinetic measurements, collected in venoject type heparinized tubes, were taken at all time-points, but 30 and 15 min before application. Following centrifugation within 60 min of collection the plasma was transferred to polypropylene tubes and stored at −20°C until assayed.

Bioanalysis

The concentration of lidocaine base, prilocaine base, and *o*-toluidine in plasma was determined by gradient liquid chromatography and mass tandem spectrometry with electrospray ionization and selected ion monitoring. The sensitivity and robustness of the method was improved compared to previous methods (6). The limit of quantitation (LOQ) was set at 2 nmol/L for lidocaine (0.00045 mg/L), prilocaine (0.00044 mg/L) and *o*-toluidine (0.00021 mg/L). The between-day coefficients of variation (CV) for lidocaine and prilocaine were 3.4–12.1% at concentrations of 5–750 nmol/L. The between-days CV was less than 11% for *o*-toluidine at concentration levels of 10–150 nmol/L.

The metHb values were determined by a spectrophotometric method using OSM-3 (Center 1) and ABL 520 (Center 2) (Radiometer, Copenhagen). MetHb levels were measured as the total amount of hemoglobin available as metHb (0.0–100.0%). The reference value for metHb is <2% (7). The precision of OSM-3 was ±0.5% (95% confidence interval) and the inaccuracy −0.1% to 0%. ABL 520 had a precision of ±0.8% (95% confidence interval) and an inaccuracy of −0.1% to 0%. Three analyses were performed for each blood sample and their mean was used in the evaluation.

Evaluation of pharmacokinetic results and methemoglobin measurements

Non-compartmental analysis was used to estimate the individual pharmacokinetics of lidocaine, prilocaine, and *o*-toluidine using WinNonlin software version 1.5 (Pharsight Corporation, Palo Alto, Calif., USA). The peak plasma level (C_{max}) and the time to reach C_{max}(t_{max}) were obtained directly from the observed plasma levels. The terminal half-life ($t_{\frac{1}{2}z}$) was calculated as in $2/\lambda_z$, where λ_z is the slope of the log plasma concentration versus time curve determined by linear regression of the last 5 data points. Plasma levels below the LOQ appearing in terminal samples were omitted from the analysis.

The highest measured percentage of metHb after application of the gel and the time of the highest measured percentage of metHb were identified in each patient. Results were summarized using graphs and descriptive statistics.

Results

Patients

Demographics and periodontal status are summarized in Table 1. A median (min-max) total amount of 8.6

Table 1. Demographics and periodontal status in patients with generalized periodontal disease. All results are given per patient ($n = 11$)

Variable	Median (min-max)
Age	51 (26–65)
Gender (F/M)	(5/6)
Nicotine use (PS/HS/NS/Snuff)*	(3/7/1/1)
Number of natural teeth	27 (20–28)
Proportions (%) of teeth with pocket depths ≥5 mm	55 (49–69)**
Proportions (%) of teeth with pocket depths ≥6 mm	35 (23–54)**
Mean pocket depths (mm) ($n = 10$)***	4.7 (4.0–5.6)**
Proportions (%) of bleeding pockets	76 (53–100)**

* PS = previous smoker, HS = habitual smoker, NS = non-smoker.
** The percent of teeth with pocket depths ≥5 mm, the percent of teeth with pocket depths ≥6 mm, the mean probing depth and percent of bleeding pockets were calculated for each patient.
*** Missing value in one patient.

(8.0–8.7) g Oraqix, which corresponds to 215 (200.0–217.5) mg of lidocaine base and prilocaine base, respectively, was administered over a median (min-max) period of 3.0 (2.6–3.4) h. SRP was performed in median (min-max) 22 (16–27) teeth. Following reapplication of the gel in median (min-max) 10 (0–18) teeth, the SRP was interrupted due to pain in 1 (0–6) of these, whereupon SRP was continued on subsequent teeth.

Pharmacokinetic results

Lidocaine, prilocaine, and *o*-toluidine plasma concentration time curves are found in Figs 1, 2, 3, and 5; pharmacokinetic parameters for lidocaine, prilocaine, and *o*-toluidine are summarized in Table 2. The highest individual C_{max} values of lidocaine (0.55 mg/L) and prilocaine (0.18 mg/L) were reached 3.7 h and 3.3 h after start of application of the gel in the same patient.

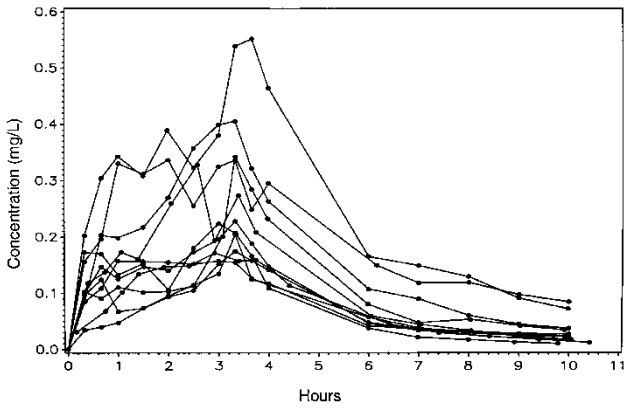

Fig. 1. Lidocaine plasma concentrations following application of 8.0–8.7 g of Oraqix® (200.0–217.5 mg of lidocaine base and prilocaine base, respectively) over 2.6–3.4 h in periodontal pockets in 11 patients with generalized periodontal disease.

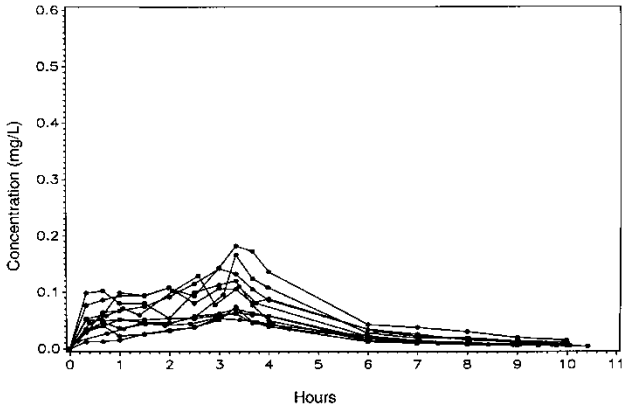

Fig. 2. Prilocaine plasma concentrations following application of 8.0–8.7 g of Oraqix® (200.0–217.5 mg of lidocaine base and prilocaine base, respectively) over 2.6–3.4 h in periodontal pockets in 11 patients with generalized periodontal disease.

Methemoglobin levels

Immediately before the start of application, the median (min-max) metHb levels were 0.77 (0.00–1.11)%. After application of the gel there was a slight increase in metHb levels and the highest measured individual values, 1.23 (0.83–1.73)%, were reached 2.6 (1.0–4.0) h after the start of application of the gel (Figs 4 and 5). All levels were below 2% and thus within reference levels.

Adverse events

There were no adverse events reported during the visual inspection performed between application of Oraqix and start of probing, neither were any signs of systemic toxicity observed in any patient. The majority of adverse events reported, in total 30, were transient events in the oral

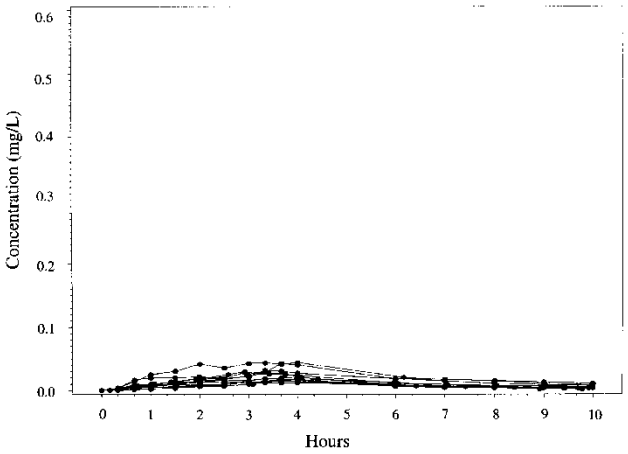

Fig. 3. *O*-toluidine plasma concentrations following application of 8.0–8.7 g of Oraqix® (200.0–217.5 mg of lidocaine base and prilocaine base, respectively) over 2.6–3.4 h in periodontal pockets in 11 patients with generalized periodontal disease.

Table 2. C_{max} and t_{max} for lidocaine, prilocaine, and *o*-toluidine following application of 8.0–8.7 g of Oraqix® (200.0–217.5 mg of lidocaine base and prilocaine base, respectively) over 2.6–3.4 h in periodontal pockets in 11 patients with generalized periodontal disease. Results are presented as mean ± *s* (standard deviation) (min-max). t_{max} is presented as median (min-max)

	C_{max} (mg/L)	t_{max} (h)	$t^{\frac{1}{2}}$ (h)
Lidocaine	0.28 ± 0.12 (0.16–0.55)	3.3 (2.0–3.7)	3.6 ± 1.3 (2.2–6.5)
Prilocaine	0.11 ± 0.04 (0.05–0.18)	3.3 (2.0–3.3)	2.8 ± 1.03 (2.0–5.7)
O-toluidine	0.025 ± 0.011 (0.013–0.044)	3.7 (1.5–4.0)	4.0 ± 1.1 (2.0–5.6)

cavity, such as soreness, redness, vesicles, and tenderness corresponding to the clinical picture normally seen in this category of patients and after SRP treatment. The instrumentation was more extensive than normally used for clinical practice, which most likely had an influence on the frequency of local reactions. In addition, overflow of the gel could not be prevented owing to the large amounts of Oraqix applied. Some patients experienced local numbness because gel had accidentally escaped on to the tongue or other parts of the mouth.

Discussion

The objective of the present study was to evaluate the potential for systemic toxicity of 5 cartridges of Oraqix applied to periodontal pockets during pocket depth probing and SRP. Patients with generalized periodontitis were included in order to document the plasma concentrations of lidocaine and prilocaine from the gel following the application of large volumes of Oraqix in patients undergoing pocket depth probing and SRP of the entire dentition. The dose, 5 cartridges of Oraqix, was applied within a period of 2.6–3.4 h. Only short breaks, necessary for the investigator and patient, were made during the SRP procedure and application of Oraqix. The gel remained within the pockets for as long as possible before the mouth was rinsed out with water half an hour after completion of the application of Oraqix and the SRP. Consequently, the present study was provocative with respect to the total dose, the dose administered over time, and the long exposure of the gel to the periodontium. It is unlikely that a total dose of 5 cartridges of Oraqix can be applied substantially faster in a clinical setting.

The highest individual peak plasma concentrations for lidocaine and prilocaine were 0.55 mg/L and 0.18 mg/L, respectively. The lower levels of prilocaine compared to those of lidocaine are in accordance with the larger volume of distribution and higher clearance for prilocaine compared to lidocaine (8). Toxic effects on the CNS generally occur at lidocaine plasma concentrations of 5–6 mg/L (9), whereas the CNS signs of prilocaine toxicity in man are briefer and less severe than following the same intravenous dose of lidocaine, probably related to differences in their disposition (10, 11). As the systemic toxicity of lidocaine and prilocaine is 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 indicate at least a 6-fold safety margin in comparison to the initial signs of CNS toxicity.

The mean terminal half-lives of lidocaine and prilocaine, 3.6 and 2.8 h respectively, were longer than

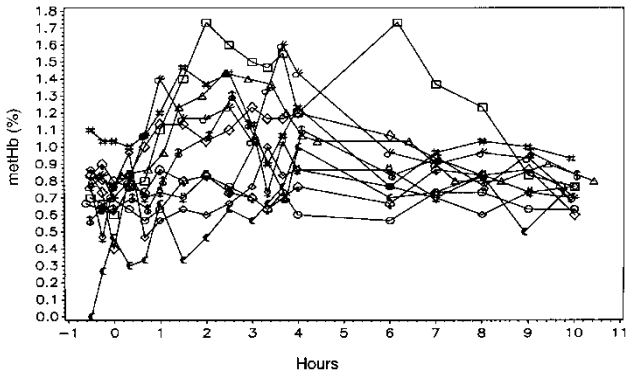

Fig. 4. Methemoglobin levels (metHb) (%) following application of 8.0–8.7 g of Oraqix® (200.0–217.5 mg of lidocaine base and prilocaine base, respectively) over 2.6–3.4 h in periodontal pockets in 11 patients with generalized periodontal disease.

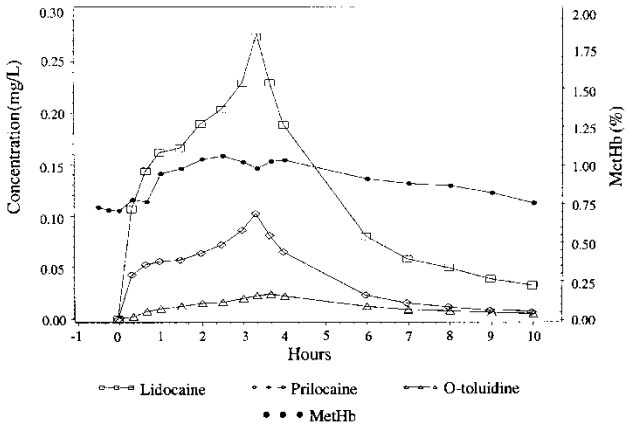

Fig. 5. Mean lidocaine, prilocaine and *O*-toluidine plasma concentrations and mean methemoglobin levels (metHb) (%) following application of 8.0–8.7 g of Oraqix® (200.0–217.5 mg of lidocaine base and prilocaine base, respectively) over 2.6–3.4 h in periodontal pockets in 11 patients with generalized periodontal disease.

reported following intravenous administration, 1.6 h for both substances (12), which reflects absorption-dependent elimination due to sustained absorption from the periodontal pockets. The peak plasma levels of lidocaine and prilocaine were reached within 1 h after completion of the Oraqix application. This was consistent with previous findings, where peak plasma levels of lidocaine and prilocaine were reached within 40 min after completion of a 6 to 9 min application of Oraqix (13). The plasma levels of lidocaine obtained in the present study were considerably lower than those obtained following intra-oral injections of Xylocaine 2% with epinephrine. An intra-oral injection of 200 mg lidocaine HCl produces peak plasma levels of about 2 mg/L (14, 15). The lower peak levels following application of Oraqix over 3 h compared to intra-oral injection are to be expected, since the amount absorbed from the periodontal pockets is likely to be lower than that from an intra-oral injection. Even if higher doses of Oraqix were administered in the present study the peak plasma levels of lidocaine and prilocaine were only just higher than those (mean 0.17 and 0.08 mg/L, respectively) obtained after application of 0.9–3.5 g of Oraqix over 6 to 9 min (13). This is to be expected because of the longer administration time in the present study.

Prilocaine in high doses (600 mg prilocaine parenterally) is known to increase the metHb levels in the blood circulation, which may cause clinical symptoms, i.e. cyanosis, characterized by a bluish-gray discoloration of the skin at metHb levels above 10% (4). Following application of 8.5 g Oraqix in the present study, metHb levels remained within reference limits (<2%). Consequently, methemoglobinemia was of no concern during treatment with Oraqix.

In conclusion, the application of 8.5 g Oraqix (5 cartridges) for 3 h to all periodontal pockets in patients with generalized periodontal disease undergoing pocket depth probing and SRP was well tolerated. Plasma concentrations of lidocaine and prilocaine were well below threshold levels for toxic effects and no signs of systemic toxicity were seen.

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