Anesth Prog 39:4–8 1992

Hypoalgesic Effect of EMLA and Lidocaine Gel Applied on Human Oral Mucosa: Quantitative Evaluation by Sensory and Pain Thresholds to Argon Laser Stimulation

Peter Svensson, DDS,* Peter Bjerring, MD, PhD,† Lars Arendt-Nielsen, PhD,‡ and Svend Kaaber, DDS, DrOdont*

*Department of Prosthetic Dentistry and Stomatognathic Physiology, Royal Dental College, Aarhus, Denmark;
†Department of Dermatology, Marselisborg Hospital, Aarhus, Denmark;
‡Department of Medical Informatics, Aalborg University, Aalborg, Denmark

Sensory and pain thresholds to argon laser stimulation were used to evaluate the analgesic efficacy and duration of a eutectic mixture of local anesthetics (EMLA) and a 2% lidocaine gel applied topically on the oral mucosa. Application of EMLA for 2 min on the tongue and gingiva increased the pain thresholds by 92.8% and 63.4% respectively. Corresponding values for lidocaine gel were 53.6% and 21.9%. Standardized variation of the EMLA application period (2, 5, and 15 min) produced significantly different analgesic profiles on the tongue but not on the gingiva. Application of EMLA for 5 and 15 min on the tongue and for 2, 5, and 15 min on the gingiva increased the pain thresholds to a predefined analgesic level (2.15 W) for 2 to 25 min. The present experimental model for assessment of oral mucosa pain is suggested to be well-suited for investigations of intraoral analgesia.

Free nerve endings associated with thin myelinated Aδ fibers and unmyelinated C fibers in the human oral mucosa provide the peripheral neuronal receptors for pain.[1] Quantitative determinations of pain perception mediated by these fiber types in the oral mucosa are made possible by application of brief argon laser stimuli.[2,3] Sensory and pain thresholds to argon laser stimulation have recently been used to quantitate analgesic profiles of topical anesthetics applied on skin, and new recommendations for clinical use have emerged from such studies.[4] Laser-induced pain also may be used to quantitate the efficacy and effect duration of topical anesthetics applied to human oral mucosa. Such analgesic profiles may be important factors when topical anesthetics are applied in clinical practice to reduce pain during injection, removal of sutures, subgingival scaling, and other potentially painful dental procedures. A topical anesthetic consisting of a eutectic mixture of local anesthetics (EMLA) has been found effective in anesthetizing the skin[5–7] and the oral mucosa.[8,9] EMLA may provide more effective analgesia of the oral mucosa than that previously reported for conventional agents.[10]

The aim of the present study was to monitor sensory and pain thresholds to argon laser stimulation in order to compare the analgesic efficacy and duration of EMLA cream and lidocaine gel applied topically on the oral mucosa, and secondly, to determine the influence of different application periods on the analgesic profile of EMLA.

METHODS

Subjects

A total of 10 volunteers participated in the study: seven women (mean age 24 yr, range 21 to 27 yr) and three men (mean age 27 yr, range 24 to 29 yr). Informed consent according to the II Declaration of Helsinki was obtained, and the study was approved by the local ethics committee. All volunteers were free of medication and neurological diseases.

Received December 12, 1991; accepted for publication April 21, 1992.

Address correspondence to Dr. Peter Svensson, Department of Prosthetic Dentistry and Stomatognathic Physiology, Royal Dental College, Vennelyst Boulevard, DK-8000 Aarhus C, Denmark.

ISSN 0003-3006/92/$5.00

Laser Stimulation

An argon laser (Spectra Physics model 168, Mountain View, California) was used as the experimental pain stimulator on the oral mucosa.[2,3] The duration of the laser pulse was 200 ms and the beam diameter was 3 mm. A 2.15-W upper limit of stimulus intensity was chosen to avoid superficial burns, and this intensity was defined as the analgesic level.

Threshold Determinations

The sensory threshold was defined as the lowest laser power (W) required to elicit the slightest perception of warmth, touch, pressure, or faint pin-prick. The pain threshold was defined as a sharp, distinct pin-prick perception. Both thresholds were calculated as a mean of five ascending and five descending series of stimulations, by which the thresholds were reached from below and above, respectively, in a modified staircase assessment regimen.[11] Repeated stimulations of identical spots in the experimental test locations were avoided to exclude a possible effect of receptor fatigue or receptor sensitization.[12] The subjects rested comfortably during the experiments in a quiet room and wore protective goggles.

Experimental Test Locations

The anterior part of the tongue and the gingival mucosa approximately 1 mm apical to the margin of the labial gingiva of the four lower incisors were exposed to argon laser stimulation.

Topical Anesthetics

Two types of topical anesthetics were investigated: (1) a eutectic mixture of local anesthetics (EMLA, Astra, Södertälje, Sweden), which consists of 25 mg/mL lidocaine and 25 mg/mL prilocaine base in an oil-in-water emulsion, and (2) a 2% lidocaine gel. One gram of each cream or gel was applied on the experimental test locations. Hence, absorption of the amide anesthetics could not exceed 100 mg during any one experiment.

Experimental Procedures

Preliminary thresholds were monitored prior to baseline determinations in order to train the subjects and reduce anxiety over the experimental set-up.[3] The experimental test locations were dried with a gauze swab, and the cream or gel was applied using a sterile cotton tip applicator. During the application period the subjects sat on a chair with a saliva ejector placed in the corner of the mouth and cotton rolls in the lower labial fold. Efforts were made to control the placement of the topical anesthetics during the period of application. In case of displacement due to movement of the tongue, additional agent was instantly applied. At the end of the application period, the subjects expectorated and rinsed the mouth carefully with water, and the experimental locations were cleaned by a gauze swab. This procedure lasted approximately 15 to 30 sec. Immediately afterwards the first threshold was determined at time 0. Thresholds were then determined after 2, 5, 10, 15, 20, 25, and 30 min. The subjects participated in the investigation on 4 separate days in order to evaluate three different application periods (2, 5, 15 min) of EMLA and 2 min of lidocaine gel. The period of application was randomized between the experimental days in a balanced way. Both the gingiva and the tongue were tested the same day.

Statistics

Friedman's analysis of variance and Wilcoxon's signed-rank test for paired samples were used for statistical analysis. Significance was accepted at a 5% level (two-tailed). Median threshold values were also calculated.

RESULTS

Analgesic Onset

The sensory and pain thresholds on the tongue and gingiva were significantly increased after application of the topical anesthetics (Figure 1). For all application periods the highest sensory and pain thresholds were obtained immediately after removal of the topical anesthetics, and no delayed increase was observed.

Analgesic Efficacy

The increase in threshold was related to the type of anesthetic and the application period. The sensory and pain thresholds on the tongue and gingiva were significantly higher for up to 20 min after the 2-min EMLA application compared with the 2-min lidocaine application (Figure 1). The percentage increases over baseline in sensory and pain thresholds after application of EMLA for 2 min also were significantly higher than the increases after the 2-min lidocaine gel application (Table 1). For different EMLA application periods on the tongue, there was an overall positive relationship between the duration of anesthetic exposure and the intensity of effect. Both the sensory and pain thresholds were significantly more elevated at time 0 with respect to baseline for the 15-min treatment time than for the 2-min treatment time (Table 1). Mixed results were obtained with the 5-min application time. Whereas

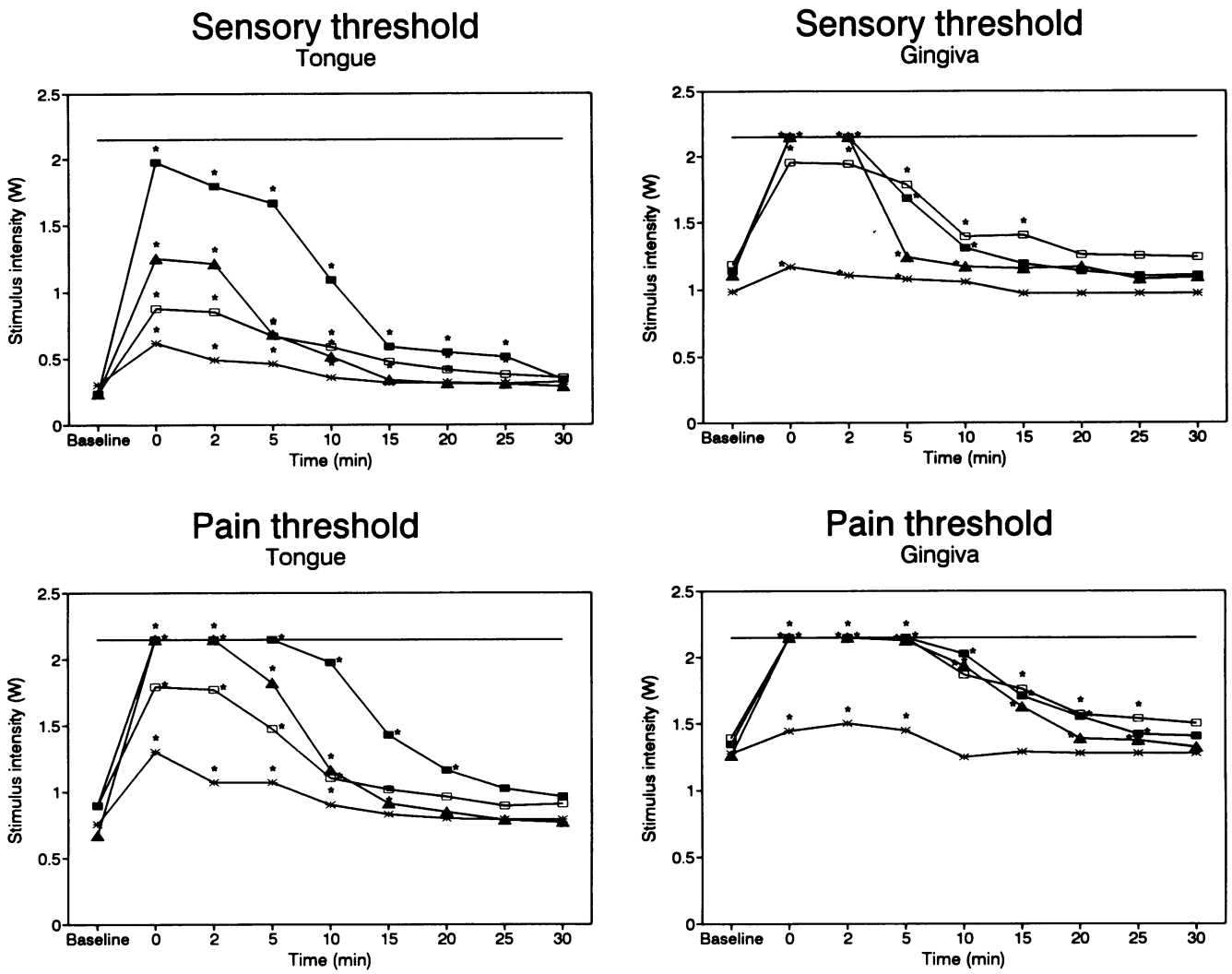

Figure 1. Median sensory and pain thresholds (W) of tongue and gingival mucosa at baseline and at 0, 2, 5, 10, 15, 20, 25, and 30 min postapplication time. EMLA was applied for 2 min (⇔), 5 min (▲), and 15 min (■), and lidocaine gel for 2 min (✳), in 10 subjects. Asterisks indicate a significant difference ($P < 0.05$) from baseline. Horizontal line represents the analgesic level, an arbitrarily chosen stimulus (2.15 W) below which tissue damage does not occur.

the percentage increase in sensory threshold at time 0 was significantly less than the 15-min value, there was no discernible difference in pain threshold. On the gingiva, the highest percentage increases over baseline occurred after the 5-min application, and there was no statistical difference between the various EMLA treatment regimens.

During the remaining 25 min, significant differences in both sensory and pain thresholds on the tongue were observed between the three different application periods of EMLA (Friedman: $P = 0.024$), with the highest thresholds caused by the 15-min application (Figure 1). However, on the gingiva, global differences in sensory or pain thresholds after the three application periods were not significant (Friedman: $P = 0.091$).

Analgesic Duration

For all application periods the sensory and pain thresholds were elevated significantly up to 25 min after removal of the EMLA on both the tongue and the gingiva. The thresholds declined most rapidly, by approximately 0.1 W/min, during the first 10 min.

The duration of the analgesic level varied with the application period and the type of topical anesthetic. Only one subject reached the analgesic level after application of

Table 1. Increase Above Baseline in Sensory and Pain Thresholds Immediately After Application of EMLA and Lidocaine

Treatment	Sensory Threshold[a] (% Increase)	Pain Threshold[a] (% Increase)
Tongue		
Lidocaine, 2 min	95.0 (53.9– 172.7)	53.6 (38.9– 72.3)
EMLA, 2 min	259.3 (153.9– 381.4)	92.8 (79.3–129.0)
EMLA, 5 min	489.7 (339.7–1046.9)	179.2 (165.0–276.8)
EMLA, 15 min	1070.9 (386.5–2453.5)	153.5 (116.4–289.5)
Gingiva		
Lidocaine, 2 min	18.5 (11.8– 30.8)	21.9 (13.0–29.5)
EMLA, 2 min	70.3 (48.3– 82.7)	63.4 (41.5–70.7)
EMLA, 5 min	87.4 (64.3–110.5)	80.2 (52.0–86.2)
EMLA, 15 min	75.0 (38.4–101.5)	68.9 (55.1–82.9)

[a] All thresholds were significantly increased over baseline ($P < 0.05$). Vertical bars indicate groups with statistically similar thresholds.

lidocaine gel on the gingiva (Table 2). The number of subjects with pain thresholds at the analgesic level on the tongue increased as the EMLA application period increased. The median duration at the analgesic level on the tongue was up to 10 min. On the gingiva nine subjects had pain thresholds at the analgesic level after every EMLA application, and the median duration at the analgesic level was 10 min (Table 2).

DISCUSSION

The present results indicate a very fast penetration of topical anesthetics through the oral mucosa, as an application period of only 2 min was sufficient to increase the thresholds significantly (Figure 1). However, elevation of thresholds to experimental pain stimulation indicates a hypoalgesic effect and not necessarily clinical analgesia. In this study, the analgesic level was arbitrarily defined as a laser intensity of 2.15 W, which prior to application of the topical anesthetics elicited a very strong and intense pin-prick perception. This finding suggests that the defined analgesic level may be close to clinical analgesia. Hence, according to the definition of analgesia, onset with EMLA was 2 min for the gingiva and 5 min for the tongue. Similar short onset times, between 5 and 7 min, have been reported for clinical analgesia of the genital mucosa.[13] Haasio et al[9] found that the highest thresholds to painful electrical stimulation of the upper gingival margin were reached 13 ± 8 min after application of EMLA. The later onset compared with the onset observed in the present study could be due to the modality of experimental pain stimulus, as electrical stimulation activates both thick (Aβ) and thin (C, Aδ) nerve fibers. Local anesthetics are known to block clinically the formation and transmission of action potentials in thin fibers before they affect thick fibers.

The increases in sensory and pain thresholds on the tongue were dependent on the application period, with the lowest increases consistently found for the shortest application period (Table 1). This relationship is in agree-

Table 2. Incidence and Duration of Sensory and Pain Thresholds at Analgesic Level

	Sensory Threshold		Pain Threshold	
Treatment	Subjects (n)	Duration[a] (min)	Subjects (n)	Duration[a] (min)
Tongue				
Lidocaine, 2 min	0	—	0	—
EMLA, 2 min	0	—	2	5 (5–5)
EMLA, 5 min	1	5 (5–5)	7	5 (2–15)
EMLA, 15 min	3	2 (2–2)	10	10 (5–15)
Gingiva				
Lidocaine, 2 min	0	—	1	5 (5–5)
EMLA, 2 min	2	10 (10–10)	10	10 (2–15)
EMLA, 5 min	7	5 (2–15)	9	10 (2–15)
EMLA, 15 min	3	5 (5–25)	10	10 (2–25)

[a] Median values are shown (with range of durations).

ment with application studies of EMLA on the hand, cubital fossa, and back.[7] On the gingiva, the increases in both the sensory and pain thresholds after the three different application periods were at the same level; no statistically significant difference was found between the thresholds, presumably because the analgesic level was reached within the application period.

Anesthetic efficacy is influenced by the vascular absorption rate and the vascular flow.[7,14] Hence, the fast onset of analgesia, no delay in effect, and the rapid decline of analgesia found in the present study may be ascribed to the high vascular flow in the oral mucous membrane. The analgesic profile after EMLA application on the oral epithelium is similar to the profile described on the facial skin, which also has a high vascular flow.[7,15]

Pain thresholds at the analgesic level were maintained up to 10 min on both the tongue and the gingiva (Table 2), indicating a short but sufficient working period for dental procedures, such as subgingival scaling of a single tooth or removal of sutures.

In conclusion, this study demonstrates the applicability of the oral argon laser stimulation technique to monitor the efficacy and duration of topical anesthetics. The analgesic efficacy after a 2-min application of EMLA is better than after a 2-min application of 2% lidocaine gel. EMLA applied for 5 min on the tongue and for 2 min on the gingiva produced adequate analgesia for 5 and 10 min, respectively. Prolongation of the application period on the tongue increases the analgesic efficacy, probably due to the formation of an analgesic reservoir between the filiform papillae.[4,16]

ACKNOWLEDGMENT

This investigation was supported in part by The Danish Dental Association's Calcin Foundation.

REFERENCES

1. Sessle BJ: The neurobiology of facial and dental pain: Present knowledge, future directions. J Dent Res 1987; 66:962–981.

2. Arendt-Nielsen L, Bjerring P: Sensory and pain threshold characteristics to laser stimuli. J Neurol Neurosurg Psychiatry 1988;51:35–42.

3. Svensson P, Bjerring P, Arendt-Nielsen L, Kaaber S: Variability of argon laser-induced sensory and pain thresholds on human oral mucosa and skin. Anesth Prog 1991;38:79–83.

4. Arendt-Nielsen L, Bjerring P: Laser-induced pain for evaluation of local analgesia: a comparison of topical application (EMLA) and local injection (lidocaine). Anesth Analg 1988; 67:115–123.

5. Juhlin L, Evers H, Broberg F: A lidocaine–prilocaine cream for superficial skin surgery and painful lesions. Acta Derm Venereol (Stockh) 1980;60:544–546.

6. Juhlin L, Evers H: EMLA: A new topical anesthetic. Adv Dermatol 1990;5:75–92.

7. Arendt-Nielsen L, Bjerring P, Nielsen J: Regional variations in analgesic efficacy of EMLA. Acta Derm Venereol (Stockh) 1990;70:314–318.

8. Holst A, Evers H: Experimental studies of new topical anaesthetics on the oral mucosa. Swed Dent J 1985;9:185–191.

9. Haasio J, Jokinen T, Numminen M, Rosenberg PH: Topical anaesthesia of gingival mucosa by 5% eutectic mixture of lignocaine and prilocaine or by 10% lignocaine spray. Br J Oral Maxillofac Surg 1990;28:99–101.

10. Rosivack RG, Koenigsberg SR, Maxwell KC: An analysis of the effectiveness of two topical anesthetics. Anesth Prog 1990;37:290–292.

11. Gracely RH, Lota L, Walter DJ, Dubner R: A multiple random staircase method of psychophysical pain assessment. Pain 1988;32:55–63.

12. Laitinen LV, Ericksson AT: Electrical stimulation in the measurement of cutaneous sensibility. Pain 1985;22:139–150.

13. Ljunghall K, Lillieborg S: Local anaesthesia with lidocaine/prilocaine cream (EMLA®) for cautery of condylomata acuminata on the vulval mucosa. The effect of timing of application of the cream. Acta Derm Venereol (Stockh) 1989; 69:352–356.

14. Juhlin L, Hägglund G, Evers H: Absorption of lidocaine and prilocaine after application of a eutectic mixture of local anesthetics (EMLA) on normal and diseased skin. Acta Derm Venereol (Stockh) 1989;69:18–22.

15. Nielsen JC, Arendt-Nielsen L, Bjerring P, Svensson P: The effect of EMLA cream on facial skin: quantitative evaluation using argon laser stimulation. Acta Derm Venereol (Stockh) 1992;72:281–284.

16. Evers H, von Dardel O, Juhlin L, Ohlson L, Vinnars E: Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA): Studies in volunteers. Br J Anaesth 1985;57:997–1005.