VASCULAR RESPONSE OF HUMAN SKIN AFTER ANALGESIA WITH EMLA CREAM

P. BJERRING, P. H. ANDERSEN AND L. ARENDT-NIELSEN

Recently, a Eutectic Mixture of the Local Analgesics lignocaine and prilocaine (EMLA) was introduced for percutaneous analgesia before venepuncture [1-3], removal of genital warts [4] or molluscum contagiosum [5], and for split skin grafting [6]. The cream (in which the oil phase contains 2.5% lignocaine and 2.5% prilocaine) is applied on the skin surface under a plastic film occlusion for at least 1 h before the painful procedure. Clinically, blanching, erythematous skin responses, or both, have been observed in skin areas treated with EMLA cream [5, 7, 8].

In the present study, dermal vascular responses were monitored quantitatively by reflectance spectrophotometry after different application times of EMLA cream, placebo EMLA cream, moisturizing cream or plastic occlusion.

MATERIALS AND METHODS

Volunteers

We studied nine healthy volunteers (four male, five female; mean age 33 yr (range 26-44 yr)) with no previous history of skin disease. All volunteers were free of medication and all gave their informed consent. The study was approved by the local Ethics Committee.

Vascular dynamics after different EMLA application times

EMLA (Astra, Sweden) and placebo cream were applied on symmetrical test areas on the ventral surface of the forearms under plastic occlusion (Tegaderm, 3M) for 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h. The test sites were 10 cm² in area, and 2.5 g of cream was applied to each location. All applications were carried out in one session. Five minutes after the removal of the creams and plastic film occlusion, the spectral skin reflectance was recorded; measurements were repeated every 1 h until 3.5-4 h after removal of the cream. After 18 h, clinical examination of skin reactions was made.

Comparison of EMLA cream, placebo cream, moisturizing cream and plastic film occlusion

The application times which had produced maximal blanching and maximal erythema were used for comparison of the vascular effects of:

(1) EMLA cream, composed of lignocaine, prilocaine, Arlatone 289, carboxypolymethylene, sodium hydroxide to pH 9.2, and water.

(2) EMLA placebo cream which consisted of the same ingredients as EMLA, without the analgesics, which were substituted by fractionated coconut oil. The oil:water ratio was approximately 1:9.

(3) A moisturizing cream which consisted of
Fig. 1. Erythema index (EI) determined after 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h application of EMLA cream (hatched areas) on the forearms. The EI was determined every 1 h after the cream was removed. Negative values of EI indicate relative skin blanching, positive values erythema compared with initial skin colour.
petrolatum, cetanol, monolein, lanolin, citric acid, sodium hydroxide, and water, with a pH of 5, and an oil:water ratio of approximately 1:1.

(4) An occlusive plastic film (Tegaderm, 3M).
All test substances were applied on the ventral aspect of the middle part of the forearm.

Objective monitoring of skin vascular responses

Reflectance spectroscopy. Changes in skin blood content were measured by reflectance spectrophotometry on symmetrical skin sites, 7 cm² in area, in the centre of the test site. The spectral reflectance of incident light in the range 350 nm (u.v.-A) to 675 nm (dark red) was recorded by a specially constructed fibreoptic scanning reflectance spectrophotometer controlled by a microcomputer [9]. The spectral reflectance recordings were performed within 20 s, and the measurements had a high reproducibility (coefficient of variance = 0.2%).

The absorbance of light by haemoglobin in the upper dermal vascular plexus was calculated from skin reflectance spectra and expressed as an “erythema index” (EI) [10]. EI is a relative measure of blood content in the upper dermis, and it correlates well with clinical assessment of erythema or blanching. However, the erythema index is a more sensitive and reproducible method for quantification of erythema than subjective assessment of erythema [9].

Skin blood flow. Cutaneous blood flow was monitored by laser Doppler flowmetry (Periflux, Perimed, Sweden) on the test areas and adjacent, untreated control areas outside the adhesion area of the plastic film, before and after an application time of 1, 1.5, 2, 3, 4, 5 and 6 h. Alterations in blood flow values on the treated areas were normalized according to small changes in skin blood flow measured on the control area during the experiment.

Statistics
Data were analysed by Wilcoxon’s test. P < 0.05 was considered significant.

RESULTS

There was a vascular response after application of EMLA cream under plastic occlusive film with initial blanching and later erythema (fig. 1). For application times of 0.5–1.5 h, increasing vasoconstriction was observed (fig. 2, A). The reaction was measured quantitatively by reflectance spectroscopy as a decrease in EI. The skin colour (degree of erythema) of the volunteers before the test started was standardized to EI = 0. After only 0.5 h, the EI was reduced significantly compared with the initial value (P = 0.05). After 1.5 h of application, EI was reduced maximally to —13.8 arbitrary units (P < 0.02). Application times of 3 h and longer were associated with erythema (fig. 2, B). At 3 h, this erythema was not present immediately after removal of the cream, but it developed after an additional 2-h observation period. However, after applications of EMLA for 4 h or longer, the erythema was present immediately after removal of the cream. This reaction was visible after 5 h and 6 h of EMLA application (fig. 3). For all application times longer than 2 h, the EI continued to increase after the cream was removed. Maximal erythema with an EI of 40 arbitrary units was obtained 4 h after a 6 h application (fig. 1). Subsequently there was no further increase in EI. The erythema subsided within 18 h except in one volunteer who developed an urticarial reaction at the 6-h application area. In this volunteer, the skin area was normal after 24 h and the reaction could not be reproduced.

Applications of EMLA cream for different times resulted in a biphasic response in skin blood flow. After 1.5 h, blood flow was reduced maximally to 62.3% of the pre-treatment value, and after 6 h blood flow increased to 148%.

After 1.5 h application, significant vasoconstric-
FIG. 3. After application of EMLA cream for 6 h, skin erythema increased after removal of cream, presumably because of formation of an intracutaneous depot of local analgesics. 1 = Immediately after cream removal; 2 = after 1 h; 3 = after 2 h; 4 = after 3 h.

Decrease (decrease of EI) was produced not only by EMLA ($P < 0.02$), but also by placebo EMLA and the moisturizing cream ($P < 0.05$). The plastic film occlusion alone did not alter EI significantly. Four hours after a 6 h application, only EMLA cream produced clinical erythema ($P < 0.02$) (table I).

Both EMLA, placebo and moisturizing creams reduced blood flow maximally at 1.5 h of application, to 62%, 63% and 79%, respectively. In contrast with EMLA cream, the other creams did not increase blood flow above the initial value after longer application times. The plastic film did not alter blood flow significantly.

Mean skin blood flows were correlated with mean EI ($r = 0.96$).

DISCUSSION

Vascular reactions after different EMLA application times

Juhlin, Evers and Broberg have described blanching of the skin immediately after 30 or 60 min application of EMLA cream [5] without local irritation. Later, Juhlin and Rollman [7] described redness and oedema in patients with atopic eczema after 30-60 min of EMLA application, but no reaction was observed in normal controls.

In the present study, blanching was observed in normal skin after 30-60 min application of EMLA. Evers and colleagues [8] described temporary pallor, but no sign of local "irritation" except for two cases of slight redness after 24 h of EMLA application. This contrasts with the present study in which all volunteers developed substantial erythema after EMLA applications longer than 2 h. These differences may be caused by the long application time (24 h) in the study by Evers, as the analgesics in epi- and intracutaneous depots were washed out by the dermal blood flow, and by the measurement of skin reactions immediately after removal of the cream. This procedure may miss late reactions.

The vascular reactions were faster in patients with atopic dermatitis and eczematous skin diseases [7]. Blanching was observed after 5-15 min and erythema after 30-60 min of application of

| TABLE 1. Mean Erythema Index of the skin before and after application of EMLA cream, placebo EMLA and moisturizing cream under plastic film occlusion and plastic film occlusion alone. The application times were 1.5 h with immediate reading, and 6 h followed by reading after 4 h (10 h). All creams produced initial blanching, but only EMLA produced later erythema. $P$ values are for differences from values before application. |
|---------------|----------------|-----------------|-----------------|----------------|
|               | EMLA cream     | Placebo EMLA cream | Moisturizing cream | Plastic film occlusion |
| Before application | 8.6            | 10.8            | 12.4            | 13.8 |
| After 1.5 h application | 3.2            | 3.0             | 5.3             | 18.5 |
| Blanching      | $P < 0.02$     | $P < 0.05$      | $P < 0.05$      | ns  |
| 4 h after a 6-h application | 41.3           | 12.5            | 13.8            | 16.2 |
| Erythema       | $P < 0.02$     | Normal          | Normal          | Normal |
| ns             | ns             | ns              | ns              | ns    |
VASCULAR RESPONSE AFTER EMLA CREAM

EMLA. This may be the result of increased penetration of analgesics in abnormal skin.

In the present study, blanching and erythema developed as a biphasic reaction only with EMLA cream (fig. 2, table I). This biphasic vascular reaction may explain previous reported differences in skin reactions after EMLA cream [5, 7, 8]. The cause of the biphasic reaction is still not known. Intracutaneous cumulation of local analgesics during application under occlusion and a subsequent wash-out and reactive hyperaemia may be responsible (fig. 3).

Comparison of EMLA cream, placebo cream, moisturizing cream and occlusion film

The vascular responses produced by EMLA cream, placebo EMLA cream, moisturizing cream, and plastic film occlusion were monitored by EI immediately after a 1.5-h application (at maximal blanching) and 4 h after a 6-h application (for maximal erythema). All creams produced maximal blanching and only the plastic film occlusion did not alter the vascular state of the skin. These creams differed in composition: the EMLA placebo consisted of more than 90% water, with carboxypolymethylene to increase viscosity, emulsifier and an inert oil, whereas the moisturizing cream consisted of petrolatum, emulsifiers, citric acid, sodium hydroxide and water.

The observed blanching might be caused by stimulation of the vascular musculature, either directly or by selective stimulation of the vascular innervation. This reaction is not observed normally after use of moisturizers, which are not usually used under occlusion. The effect was visible after 30–60 min of application under occlusion, measured as a decrease in EI after 30 min. The pH of EMLA cream and placebo EMLA cream was 9.2. A high pH might alter the ionic balance in the nerve membranes in the upper skin layers, leading to vasoconstriction, but the pH of the moisturizing cream was 5, and this cream had vascular effects identical to those of EMLA and placebo EMLA cream. This eliminates both pH and the oil:water ratio in the cream emulsions as significant causative factors.

Blanching of the skin might be induced by cumulation of water or lipids in the epidermis. Both change the optical properties of the epidermis, mimicking vasoconstriction when measured by reflectance spectroscopy. Therefore, skin blood flow was measured also. After application for 1.5 h, all creams tested reduced cutaneous blood flow maximally.

Both lignocaine and prilocaine have concentration-dependent vasoconstrictor and dilator properties [11, 12]. Blanching occurs at lower, and erythema at higher concentrations. After short applications of EMLA cream, lower concentrations may occur in the dermis [13], and longer application times may increase the concentration of analgesics in the vascular plexus of the upper dermis, resulting in vasodilatation. In the present study, application of 2 h was sufficient to produce erythema, when observed 2 h after removal of the cream. The delayed erythema after 2- and 3-h application may have been caused by an initial superficial cumulation of local anaesthetics in the epidermis, which during the subsequent observation time penetrated slowly to the vascular layers of the skin.

Erythema was present immediately after removal of the cream at application times of 4 h or longer. The erythema was more intense when EMLA was applied for 2 h with a subsequent observation time of 2 h, than after a 4-h application with immediate recording of the erythema after removal of the cream. This accords with the findings of Willatts and Reynolds [13], who observed more pale reactions after injections of lignocaine in low concentrations (0.1%) than in higher concentrations (0.33%). At higher concentrations, prilocaine produced erythema while lignocaine produced only a minor decrease in the pale reaction. Hyperaemia of the skin has been described after topical application of analgesic formulations containing ketocaine [14]. The vascular reaction was suggested to be the result of a relaxant effect on the vascular smooth muscle after blockade of Ca\(^{2+}\) entry channels by the cationic form of local analgesics [15, 16].

REFERENCES