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Plasma Concentrations and Analgesic Effect of EMLA® (Lidocaine/Prilocaine) Cream for the Cleansing of Leg Ulcers

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Plasma concentrations of lidocaine and prilocaine were assessed in 8 patients after the application of 8–10 g EMLA® 2% cream for 60 min to leg ulcers measuring 31–80 cm². Maximum individual plasma concentrations were 205 ng/ml for lidocaine and 79 ng/ml for prilocaine, which is twenty times lower than those associated with toxicity. The analgesic effect of EMLA 2% and 5% cream for the surgical cleansing of leg ulcers was compared in a double-blind, four-period, cross-over study in 10 patients. The ulcer was covered with a thick layer of cream for 30 min before four consecutive debridements 1–4 days apart. While the 2% and 5% creams had similar analgesic effects post-cleansing pain tended to be more frequent with the 2% cream.

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The removal of dead tissue and slough is important for the healing of leg ulcers (1, 2). Surgical cleansing (e.g. with a curette) is often necessary, but is usually a very painful experience for the patient. The pain may prevent the desired cleansing and may cause primary health centres to refer patients for hospital treatment.

A eutectic mixture of lidocaine and prilocaine (EMLA® cream) has been shown to provide anaesthesia for superficial surgical procedures involving the skin (3) and the genital mucosa (4, 5). Holm et al. reported that EMLA 5% cream applied to leg ulcers for 30 min significantly reduced the pain from debridement compared with placebo cream (6). The present study was performed to determine plasma levels of lidocaine and prilocaine after the application of EMLA 2% cream to leg ulcers, and to compare the analgesic effect of EMLA 2% and 5% cream for the surgical cleansing of leg ulcers.

PATIENTS AND METHODS

Patients

Plasma concentrations were assessed in 1 man and 7 women aged 60–83 years with leg ulcers measuring 31–80 cm². The primary etiology of the ulcers was arterial disease (1 patient), arteriovenous 2, venous 2 and immunological disease 3 patients. The duration of the ulcer symptoms was 1 to 10 years. One ulcer was located on the malleolus and 7 on the lower leg.

In a double-blind study, analgesic efficacy ws assessed in 1 man and 9 women (aged 48–84) with ulcers measuring 2–18 cm². Six patients had ulcers of venous origin and 4 patients of immunological origin. Ulceration had persisted for 0.5–38 months. Three ulcers were located on the malleolus and 7 on the lower leg.

The size of the ulcer was mesured by projecting the outline of the ulcer on a transparency, cutting out the wound map and using the weight as a function of wound size. Concomitant medication with analgesics or anti-inflammatory agents was continued throughout the study in 5 patients in the plasma study and 5 patients in the double-blind study.

Anaesthetic and surgical procedure

After removal of the bandage, a thick layer of cream was applied to the ulcer and covered with a plastic wrap (Glad®, First Brands, W. Germany). Sterile EMLA 2% and 5% cream (Astra AB, Södertälje, Sweden), containing 10+10 mg or 25+25 mg of lidocaine and prilocaine per gram, was used. The dose of cream given was calculated by weighing the tube before and after the application of the cream. The cleansing, which was performed with curettes, was started within 7 min after removal of the cream and its duration was recorded.

Plasma concentration study

8–10 g EMLA 2% cream was applied for 60 min. Blood samples were drawn from an antecubital vein into heparinized vacuum tubes (Venoject®, Terumo) before the application of EMLA and at 60, 90, 120, 150, 180 and 240 min after the application of the cream. The blood samples were centrifuged and the plasma transferred into plastic tubes (Cryotube®, Nune) and stored at −20°C until analysed by gas chromatography-mass fragmentography. The sensitivity of the assay was 10 ng/ml lidocaine or prilocaine.

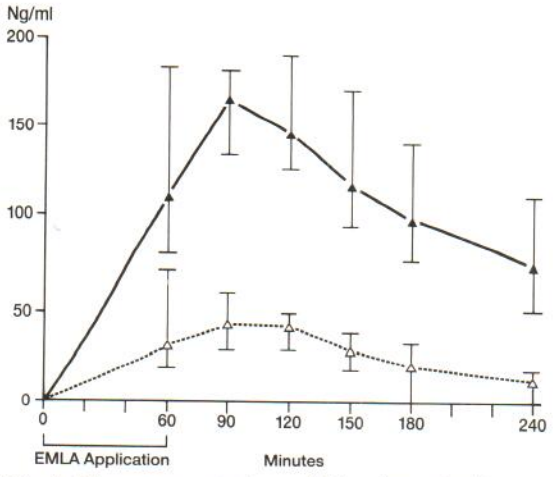

Fig. 1. Plasma concentrations of lidocaine and prilocaine following the application of 8–10 g EMLA 2% for 60 min to leg ulcers measuring 31–80 cm^2 (median and 93% non-parametric confidence limits, $n = 8$). ▲, lidocaine; △, prilocaine.

Double-blind study

In a double-blind, four-period, cross-over study 10 patients were randomly allocated to 2% and 5% EMLA cream. The randomization was balanced after two treatments; each patient received both concentrations once during the first and second treatment, and once during the third and fourth treatment. The cream was to be applied for 30 min before four consecutive cleansings, 1–4 days apart. One patient was treated with EMLA 2% for 62 min in period 2.

Clinical assessment

In both studies the pain experienced from the cleansing was rated by the patient on a 100 mm horizontal ungraded line (visual analogue scale, VAS) where 0 mm indicated 'no pain' and 100 mm 'severe pain' (7) and on a verbal scale as no pain, slight, moderate, or severe pain. The investigator recorded whether satisfactory cleansing was possible, having regard to the patient's pain reaction. The occurrence of post-cleansing pain was recorded.

The patient was asked about local irritation, particularly any burning sensation or itching, before the start of the cleansing. The physician examined the ulcer for erythema, oedema or any other reaction caused by the applied cream. The assessments were rated as none, mild, moderate, or severe.

Pharmacokinetics and statistics

The areas under the plasma concentration versus time curve (AUC) were calculated by the trapezoidal rule from time 0 to 240 min. Maximum plasma concentrations (C_{max}) were determined. The correlations between C_{max} and ulcer area, and between AUC and ulcer area, were calculated by linear regression.

In the double-blind study the differences in VAS scores between EMLA 2% and 5% were analysed with the Wilcoxon matched-pairs test. The presence of a period effect between the four treatments was tested by analysis of variance of the VAS scores. Differences in verbal pain assessment and post-cleansing pain between EMLA 2% and 5% were analysed with the sign test.

RESULTS

Plasma concentration study

The dose given corresponded to 1.2 to 2.8 g of EMLA 2% (median 1.8 g) per 10 cm^2 of ulcer. The plasma concentrations of lidocaine and prilocaine are shown in Fig. 1. The highest individual concentrations were 205 ng/ml lidocaine in a patient with an arterial ulcer measuring 56 cm^2, and 79 ng/ml prilocaine in a patient with an arteriovenous ulcer measuring 36.6 cm^2.

In 2 patients where the C_{max} values were observed after 60 min the ulcer was of arterial or arteriovenous origin, while in patients with venous disease or rheumatoid arthritis peak plasma levels were reached at 120 min after application in 4, and at 90 min in one patient. The results suggested a possible correlation between the area of the ulcer and C_{max} of lidocaine ($r = 0.64$, $p = 0.089$, Fig. 2), but not of prilocaine ($r = 0.18$, $p = 0.68$).

The correlation coefficients between AUC and ulcer area were for lidocaine $r = 0.55$ ($p = 0.16$), and for prilocaine $r = 0.17$ ($p = 0.69$). The median AUC amounted to 427 (228–540) and 103 (0–185) μg per hour/1 for lidocaine and prilocaine, respectively.

The duration of the cleansing in the plasma study was 4–11 min, and 3 patients reported no pain, 2

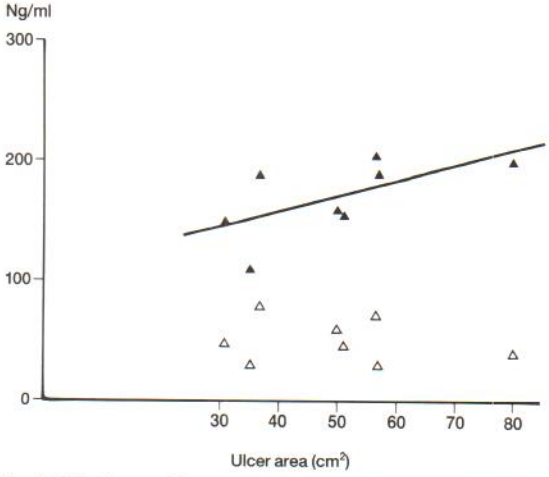

Fig. 2. Maximum plasma concentrations of lidocaine ($r = 0.64$, $p = 0.089$) and prilocaine ($r = 0.18$, $p = 0.68$) vs. ulcer area following the application of 8–10 g EMLA 2% for 60 min. ▲, lidocaine; △, prilocaine.

slight pain and 3 moderate pain during the surgical procedure. The median VAS pain score was 18 (1–97). The investigator considered cleansing to be satisfactory in 7/8 patients. Five out of 8 patients reported post-cleansing pain.

Double-blind study

In the double-blind study the duration of cleansing was comparable for all four treatments, (median 3–4 min range 1–6 min). The dose of cream given per area was comparable for the four treatments, but with variations between patients, the median of the four doses given to each patient being 0.75 to 9.0 g (median 2.9 g) per 10 cm^2 of ulcer.

There was a similar analgesic effect for the 2% and 5% creams. The patients felt no or only slight pain in 80–90% of the treatments, and no patient felt severe pain. The median VAS pain scores were 5–14 out of 100. The pain during the 3rd and 4th debridements was lower than during the 1st and 2nd debridements ($p = 0.039$).

The investigator considered cleansing to be satisfactory in all patients except for the two first treatments in a patient with diabetes. Pain subsequent to treatments 1 or 2 was reported by 8/10 patients when given 2% EMLA and 4/9 patients when given 5% EMLA (n.s.).

No systemic adverse reactions were observed. In the plasma study, one patient felt a slight and one patient a severe burning sensation during the 60-min application of EMLA 2% cream. Slight local pallor was observed in one patient. In the double-blind study, 3 patients reported slight burning and 1 moderate burning after EMLA 2% and 2 reported slight burning after EMLA 5%; the latter 2 patients felt burning after both concentrations of the cream. One patient felt a slight itching after both treatments with EMLA 5%. Slight redness was observed after EMLA 5% in one patient and after both 2% and 5% in another patient. Slight or moderate local pallor was observed in 3 patients.

DISCUSSION

The treatment of leg ulcers constitutes a major workload for both primary health district nurses and dermatology departments. The chronic nature of the disease necessitates between one and three visits per week during several months for ambulatory patients. In our out-patient department more than 80% of nurses' time is taken up by the treatment of leg ulcers. Treatment in hospital usually lasts 3 to 5 weeks. In 1988 the mean duration of stay at our hospital for patients with leg ulcers was 23 days compared with 11.5 days for patients with other diseases. Pain caused by the changing of dressings and the cleansing of the ulcers is common. The use of a local anaesthetic cream in this study enabled sufficient pain control and satisfactory cleansing in 95% of the treatments. Local reactions were transient and mild, except in one patient treated with EMLA 2% for 60 min, who reported an intense burning sensation.

Our results showed that EMLA 2% cream, in a dose containing 100 mg lidocaine and 100 mg prilocaine, applied to leg ulcers measuring up to 80 cm^2 for 60 min gives rise to plasma concentrations 20–35 times lower than those associated with toxicity, 5000–6000 ng/ml (8). The median prilocaine levels were only 17–30% of the lidocaine levels. A difference in plasma concentration is also observed after i.v. infusion or neural blockade, the reason being the large volume of distribution and the high clearance of prilocaine, 2.4 l/min as opposed to 0.95 l/min for lidocaine (9).

A comparison of the AUC values for prilocaine with i.v. data in volunteers (H. Evers, personal communication) indicates that following the application of EMLA 2% for 1 hour to leg ulcers approximately 15% of the dose reached the systemic circulation. Our data did not allow the corresponding comparison to be made for lidocaine.

Holm et al. assessed plasma levels after the application of 5–10 g EMLA 5% for 10–30 min to patients with venous leg ulcers measuring 3–64 cm^2. The highest individual value was 839 ng/ml of lidocaine, and C_{max} after 20–30 min application was observed after 90–150 min in 8/9 patients (6). Our results imply that in patients with ulcers of arterial origin, C_{max} may be reached earlier than in patients with venous disease. A decreased absorption rate from the dermal tissues of the legs to the systemic circulation is logical in connection with decreased venous return.

The results imply that the frequency of post-cleansing pain may be higher with the 2% than with the 5% EMLA cream, indicating a possible difference in duration of analgesia. The anaesthetic onset time of EMLA 5% on adult skin is about 60 min (10) but on the genital mucosa, only 4–5 min (5, 11). It may be that, when EMLA 5% is applied to ulcers, the onset time is shorter than 30 min which was used

in this study. The time for optimal analgesic effect on leg ulcers is currently being studied by others.

In the double-blind study the third and fourth cleansings were less painful than the first and second ones. Possible reasons for a decrease in pain with repeated treatments may be psychological, different absorption rates of the local anaesthetics or reduced wound hyperalgesia. Necroses present at the start of a treatment sequence may impair the absorption and may be more painful to remove than fibrin, pus, etc. Local anaesthetics may also have anti-inflammatory effects (12), which would decrease wound hyperalgesia.

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REFERENCES

1. Forrest RD, Gamborg-Nielsen P. Wound assessment in clinical practice. A critical review of methods and their application. Acta Med Scand, Suppl 687: 69–74.
2. Ryan TJ. Current management of leg ulcers. Drugs 1985; 30: 461–468.
3. 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.
4. Hallén A, Ljunghall K, Wallin J. Topical anaesthesia with local anaesthetic (lidocaine and prilocaine, EMLA) cream for cautery of genital warts. Genitourin Med 1987; 63: 316–319.
5. Ljunghall K, Lillieborg S. Local anaesthesia with a lidocaine/prilocaine cream (EMLA®) for cautery of condylomata acuminata on the vulval mucosa. The effect of timing of application of the cream. Acta Derm Venerol (Stockh) 1989; 69: 362–365.
6. Holm J, Andrén B, Grafford K. Pain control in the surgical debridement of leg ulcers by the use of a topical lidocaine-prilocaine cream, EMLA®. Acta Derm Venereol (Stockh) 1990; 70: 132–136.
7. Scott J, Huskisson EC. Graphic representation of pain. Pain 1976; 2: 175–184.
8. Scott DB, Cousins MJ. Clinical pharmacology of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. Philadelphia: JB Lippincott Co, 1980; Chapter 4.
9. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986; 58: 717–731.
10. Juhlin L, Evers H. EMLA: A new topical anesthetic. In: Cullen JP, ed. Advances in Dermatology 1989; 5: 75–91.
11. Rylander E, Sjöberg I, Lillieborg S, Stockman O. Local anesthesia with a lidocaine/prilocaine cream (EMLA®) for laser treatment of condylomata acuminata. A placebo-controlled study. Obstet Gyn 1990; 75: 302–306.
12. Ohlsén L, Evers H, Segerström K, Hagelqvist E, Graffman S. Local anaesthetics modifying the dermal response of irradiation. An experimental study. Acta Oncol 1987; 26: 467–476.