Chronic moderate or severe ulcer pain reported in 37–75% of patients is associated with anxiety, depression and deleterious effects on quality of life.1–3

Eutectic mixture of lidocaine and prilocaine (EMLA®; AstraZeneca UK Ltd, Luton, U.K.) cream significantly reduces the pain of sharp debridement and the occurrence of postdebridement pain.4,9 A single dose of 5–10 g repeated 1–3 times weekly for up to 15 doses results in plasma concentrations of lidocaine and prilocaine well below the threshold for signs of central nervous system toxicity (5000–6000 ng mL−1).5,10 However, concentrations of the local anaesthetics have not been assessed after daily repeated application of the maximum recommended dose (10 g) over several days.

We report a study designed to determine the plasma concentrations of lidocaine and prilocaine during repeated daily application, for 10 days, of 10 g EMLA to leg ulcers, and to evaluate the analgesic effect on chronic ulcer pain.

This open study, conducted at five departments of dermatology in Germany, was approved by the relevant local ethics committees. Patients gave written informed consent prior to participation. The protocol was submitted to the German Federal Institute for Medicines and Medical Devices, Bonn, Germany.

The toxicity of lidocaine and prilocaine is assumed to be additive. The study was designed to determine a 95% confidence interval (CI) for the 90th percentile (P90) of the added peak plasma concentrations of lidocaine and prilocaine, assuming a normal distribution. A one-sided (upper) confidence limit was used, with the objective of confirming that plasma concentrations are unlikely to approach toxic levels. In order to estimate the P90 of the maximum plasma concentration (Cmax) with a power of 90% and a probability that ≥ 99% of the Cmax values would fall below the upper confidence bound (P = 0·99),11 24 patients were required.

Patients requiring debridement had a leg ulcer for at least 6 weeks, with an ulcer surface area of at least 50 cm², and were scheduled for at least 10 days of inpatient treatment, including sharp ulcer debridement. Patients not requiring debridement instead experienced moderate or severe chronic ulcer pain.

The ulcer was rinsed with saline, after which 10 g EMLA cream, 25 mg + 25 mg g−1, was, for 10 days, applied in a thick layer daily and the ulcer covered with cling film. In patients with ulcers > 125 cm², part of the ulcer measuring 125 cm² was marked so that only this area was covered with EMLA cream. The adjacent parts of the ulcer were covered with a protective dressing, for example zinc oxide soft paste.

After 1 h, any remaining cream was wiped away and sharp debridement by a disposable curette (Stiefel, Research Triangle Park, NC, U.S.A.) performed for the first 5 days and, when indicated for achieving a clean ulcer, for up to 10 days. A clean ulcer was defined as a surface without black necroses, slough or fibrinous plaques. Between treatments a hydrocolloid ulcer dressing (Comfeel:plus®; Coloplast, Humlebaek, Denmark) or a soft silicone dressing (Mepilex®; Mölnlycke Health Care, Gothenburg, Sweden) was applied. Compression bandages were generally applied on venous ulcers.

By projecting its outline onto transparent film of known weight and calculating the ulcer area, the size of the ulcer was measured on days 1 and 10. Patients were asked standard questions each day before the application of EMLA. The first question was ‘Please rate the current intensity of the pain from your ulcer using the pain ruler’. The visual analogue scale (VAS) ruler with a slider (Flinders Medical Centre, Bedford Park, Australia) displayed a 100-mm horizontal ungraded line anchored by the words ‘no pain’ and ‘worst pain imaginable’.

Blood samples (5 mL) were drawn from an antecubital vein immediately prior to application of cream, and also 30, 60, 80, 100, 120, 140, 160, 180 and 240 min after the start of application of the first dose (day 1) and the last dose (day 10), and immediately before the start of application of EMLA on days 2, 4, 6 and 8.

Lidocaine and prilocaine were determined by reversed-phase liquid chromatography–tandem mass spectrometry with electrospray ionization in human plasma and ultrafiltration of acidified plasma. The limit of quantification was 0·49 ng mL−1 for lidocaine and 0·44 ng mL−1 for prilocaine.

The upper limit of the 95% CI for the P90 was calculated for the sum of lidocaine and prilocaine concentrations.11 In addition, the covariation between age, ulcer area, ulcer type and treatment day, and Cmax values was evaluated by regression and correlation analysis. Two-sided 95% CIs for the mean differences between days 10 and 1 were also calculated for Cmax.

The analysis of development over time of chronic ulcer pain included patients with moderate or severe pain on enrolment.
The change in pain scores for pretreatment pain over time was tested by calculating individual regression lines for pretreatment pain intensity. The hypothesis of the slope being equal to zero was then tested with a two-sided t-test.

Twenty-five patients participated, of whom 15 (60%) reported on enrolment chronic ulcer pain of moderate or severe intensity (Table 1). Eight of the 14 patients who regularly used analgesics for ulcer pain were prescribed opioids. No symptoms of systemic local anaesthetic toxicity were observed.

$C_{\text{max}}$ values observed at similar time points were similar on days 1 and 10 for lidocaine, prilocaine, and the sum of lidocaine and prilocaine concentrations (Fig. 1), with the two-sided 95% CI for each difference between day 1 and day 10 values including zero ($-69.0$ to $112.1$ ng mL$^{-1}$ for lidocaine; $-28.0$ to $32.6$ ng mL$^{-1}$ for prilocaine; and $-97.5$ to $142.2$ ng mL$^{-1}$ for the sum of lidocaine and prilocaine).

The $C_{\text{max}}$ of the sum of lidocaine and prilocaine concentrations on day 10 was $615$ ng mL$^{-1}$. The upper limit of the 95% CI for the P90 of $C_{\text{max}}$ was $1515$ ng mL$^{-1}$; the maximum $C_{\text{max}}$ observed was $1910$ ng mL$^{-1}$. The median decrease in ulcer area in the debridement group was $16.7$ cm$^2$, corresponding to 17% healing (Table 1).

The size of the ulcer area had a significant effect ($P < 0.01$) on the peak values. Increasing the ulcer area by 1 cm$^2$ resulted in an estimated increase in $C_{\text{max}}$ of $7$ ng mL$^{-1}$ for the sum of lidocaine and prilocaine. $C_{\text{max}}$ values did not depend on patient age ($P > 0.70$) or ulcer type ($P > 0.50$).

| Table 1 Patients, ulcer characteristics and ulcer area |
|---------------------------------|
| Debridement ($n = 23$) | Nondebridement ($n = 2$) | Total ($n = 25$) |
|-------|-----------------|-----------------|
| **Age (years)** | 71.0 | 59.5 | 71.0 (36.0–92.0) |
| **Male/female** | 5/18 | 1/1 | 6/19 |
| **Weight (kg)** | 85 | 78 | 85 (55–157) |
| **Ulcer aetiology (n)** | 15 | 2 | 17 |
| Venous | | | |
| Arteriovenous | 5 | 0 | 5 |
| Vasculitic | 3 | 0 | 3 |
| **Duration of ulcer(s) (months)** | 25.9 | 62.1 | 36.1 (2.0–794.0) |
| **Baseline study ulcer area (cm$^2$)** | 97.4 (62.0–160.0) | 108.4 (70.0–146.0) | 97.8 (62.0–160.0) |
| **Day 10 ulcer area (cm$^2$)$_a$** | 86.4 (54.0–129.0) | 114.4 (52.0–177.0) | – |
| **Change in ulcer area (cm$^2$)$_a$** | $-16.7$ (–83.0 to $-2.0$) | $-6.1$ (–19.0 to 31.0) | – |
| **Degree of chronic ulcer pain on enrolment (VRS)** | | | |
| None | 4 | | 0 |
| Slight | 5 | | 1$^b$ |
| Moderate | 11 | | 1 |
| Severe | 3 | | 0 |
| VAS | 56.0 (0–92.0) | | 42.5 (20.0–65.0) |
| **Degree of chronic ulcer pain, patients with moderate or severe pain on enrolment (VAS)** | | | |
| Day 1 | 75 (46–92) | | |
| Day 10 | 21 (0–72)$^c$ | | |

Values are given as median (range) unless otherwise indicated. VRS, verbal rating scale; VAS, visual analogue scale. $^a$Three patients in whom only part of the ulcer was treated with EMLA$^{TM}$ were excluded from this analysis; $^b$the patient included in the chronic pain group who reported slight pain on enrolment was excluded from the evaluation of change of ulcer-related pain over time; $^cP < 0.01$. 

Fig 1. Mean (95% confidence interval) plasma concentrations of lidocaine, prilocaine, and the sum of lidocaine and prilocaine on day 10, after daily application of 10 g EMLA$^{TM}$ cream for 60 min, for 10 days.

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Mean predose samples taken before EMLA application on days 3, 5, 7 and 9 were 29–43 mg mL\(^{-1}\) and 5.9–7.3 ng mL\(^{-1}\) for lidocaine and prilocaine, respectively, indicating minimal residual concentrations 24 h after the previous treatment.

In patients with moderate or severe chronic ulcer pain, prior to enrolment the median pretreatment VAS pain score was 75, which decreased gradually to 21 by day 10 (P < 0.001). Purcell et al. described a patient with an extremely painful (VAS score of 9/10) leg ulcer, with increasing difficulty with daily activities and poor sleep.\(^1\) EMLA applied to the ulcer and left overnight reduced the pain to a VAS score of 5/10 within the first 24 h. After 3 weeks the pain score was further reduced to 3/10, suggesting that the use of EMLA in patients with painful leg ulcers deserves further study. Parientral prilocaine HCl in doses exceeding 600 mg can cause methaemoglobinemia in adults. Ten grams of EMLA contains 250 mg prilocaine; when the remaining cream is wiped off, the bioavailability is approximately 15–25%.\(^14\) Local transient pallor (2–4%) or erythema (2–6%) of the ulcer at the removal of EMLA may theoretically be caused by the biphasic effects of local anaesthetics on vascular smooth muscle, increasing concentrations modulating constriction into dilatation;\(^15\) however, similar frequencies are observed with placebo cream.

Daily application of 10 g EMLA to ulcers of a maximum size of 125 cm\(^2\) for 60 min, combined with sharp debridement when indicated, for up to 10 days, is well tolerated. The sum of plasma concentrations of lidocaine and prilocaine shows no apparent accumulation over 10 days, with the maximum peak concentration < 40% of that associated with toxic reactions.

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