Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury

J. L. PEDERSEN, T. CALLESEN, S. MOINICHE AND H. KEHLET

Summary
Pain relief may be improved by reducing sensitization of nociceptive pathways caused by tissue injury. Such a reduction depends mainly on inhibition of local inflammatory changes and the relation between duration of nociceptive block and nociceptive input. In this study we examined if prolonged topical treatment with local anaesthetics could reduce late hyperalgesia and local inflammation after burn injury in healthy volunteers. The effects of EMLA treatment for 8 h after burn on hyperalgesia, inflammation and wound healing were compared with the contralateral placebo-treated leg for 48 h after bilateral burn injuries (15 × 25 mm, 49 °C for 5 min) in a double-blind, randomized study in 12 healthy volunteers. Wound healing was studied 1 and 2 weeks after injury. Neither mechanical nor thermal primary hyperalgesia were affected significantly by prolonged EMLA treatment. Secondary hyperalgesia and skin erythema were also not changed. Seven of 12 placebo-treated legs developed blisters, in contrast with four of 12 EMLA-treated legs. Wound healing showed no apparent differences. Our data suggest that prolonged, topical treatment with local anaesthetics did not reduce local inflammation and late hyperalgesia. (Br. J. Anaesth. 1996; 76: 806–810)

Key words
Burns. Anaesthetics local, EMLA. Pain, mechanism.

Injury causes inflammation and may lead to prolonged sensitization of nociceptive pathways. Primary and secondary hyperalgesia are well established aspects of this process. Hyperalgesia describes the phenomenon of increased pain intensity in response to normally painful stimuli [1], primary hyperalgesia refers to the changes in sensation within the injury, while secondary hyperalgesia refers to sensory changes in the undamaged tissue surrounding the injury. Several inflammatory mediators promote hyperalgesia by sensitization of nociceptors [2].

Many in vitro and animal studies have shown anti-inflammatory effects of local anaesthetics and these effects may potentiate the analgesic effect of these agents. The anti-inflammatory effects may impair the host defence, but may also improve conditions with destructive inflammation. In contrast, there are only few human reports on the anti-inflammatory effects of local anaesthetics and we have shown previously that brief (3.5 h) topical treatment with local anaesthetics before and after injury did not significantly affect inflammation after burn [3]. The aim of the study was therefore to examine if prolonged and intense treatment with lignocaine–prilocaine cream (EMLA) could reduce late hyperalgesia and other markers of local inflammation after burn injury in healthy volunteers. The treatment was initiated after the burn, as this mimics the clinical situation.

Subjects and methods
We studied 12 healthy volunteers, aged 22–47 yr (all male), after obtaining informed consent and approval from the local Ethics Committee and the Danish National Health Board. Subjects were not medically knowledgeable and were not aware of the purpose of the study.

Baseline measurements, which included assessment of skin colour, mechanical pain detection threshold (MPDT) and heat pain detection threshold (HPDT), were performed on the medial calf in both legs. After obtaining baseline measurements, thermal injury was induced on each leg. All measurements, that is skin erythema, blister formation, MPDT, secondary hyperalgesia and HPDT, were made in this order, 16, 20, 24 and 48 h after the injuries. Immediately after the injury, EMLA or placebo was applied, double-blind and randomized, to the skin and covered under occlusive dressing for 8 h after the injury. Experiments were performed in a quiet room, temperature 20–22 °C, with subjects in a relaxed and reclined position. Subjects were instructed to keep their eyes closed during all measurements so that they had no impression of the results of the measurements.

EMLA treatment
EMLA cream 2 g (2.5 % prilocaine and 2.5 % lignocaine eutectic mixture, Astra, Södertälje, Sweden) or placebo (Astra; Södertälje, Sweden) was applied in a double-blind, randomized manner to the skin and covered under occlusive dressing (Tegaderm, 3M Health Care Ltd, Leicestershire, UK) for 8 h after the injury. The cream was renewed.

JURI L. PEDERSEN, MD; TORBEN CALLESEN, MD; HENRIK KEHLET, MD, PHD (Department of Surgical Gastroenterology); STEEN MOINICHE, MD (Department of Anaesthesiology); Hvidovre Hospital, University of Copenhagen, Kettegaard Allé 30, 2650 Hvidovre, Denmark. Accepted for publication: January 24, 1996.

Correspondence to J.L.P.
3 and 5.5 h after initial application, and re-covered. Subjects were instructed to avoid physical activities that could displace the thick cream layer from the injury. The burns were performed in the afternoon and the cream was removed 8 h later (late evening). Subjects attended next morning for the first measurement, 16 h after the injury.

THERMAL INJURY

Thermal injuries were produced on the medial surface of the right and left calf with a 15 x 25-mm Peltier thermode (Thermostat, Somedic A/B, Stockholm, Sweden). The thermode (49 °C) was applied to the skin for 5 min under standardized pressure (34 mm Hg), causing first- and superficial second-degree burn injuries [4, 5]. The burn caused immediate intense stinging pain, which was followed by a moderate burning pain with a more diffuse quality during the remainder of the stimulation period. Spontaneous pain after the injury has not been observed in the model.

PRIMARY HYPERALGESIA

Mechanical pain detection threshold (MPDT) within the injured area was determined by pinprick with nine progressively rigid von Frey hairs (Somedic A/B, Stockholm, Sweden). We examined the force produced by each hair by pressing it against a balance and measured the weight it produced when the force produced by each hair by pressing it against the skin for 5 min under standardized pressure (34 mm Hg), causing first- and superficial second-degree burn injuries [4, 5]. The burn caused immediate intense stinging pain, which was followed by a moderate burning pain with a more diffuse quality during the remainder of the stimulation period. Spontaneous pain after the injury has not been observed in the model.

INFLAMMATION

In order to estimate the severity of inflammation, the intensity of erythema inside the injury was assessed with a hand-held skin reflectance spectrophotometer (Dermaspectrometer, Cortex Technology, Hadsund, Denmark) [6, 7]. The spectrophotometer provided a skin erythema index based on the absorption characteristics of green and red light in the skin. Measurements were performed in six spots within the burn injury. All values were recorded and the mean calculated. The development of blisters was recorded as present or absent. Healing of the burns was documented using a questionnaire, 1 and 2 weeks after the injury.

STATISTICAL ANALYSIS

Distribution of data was evaluated with the Shapiro Wilk test [8]. Primary mechanical hyperalgesia and secondary hyperalgesia in EMLA- and placebo-treated legs were evaluated at separate times with multiple Wilcoxon tests for paired observation with Bonferroni correction and area under the curves (AUC) for the whole observation period with Student’s t test for differences in a paired design [9]. Evaluation of primary thermal hyperalgesia and erythema was based on AUC values but analysed also using parametric two-way analysis of variance (ANOVA) for repeated measurements [8]. Minimal differences between treatments detectable in the present study with a power of 90 % and a type I error of 5 % were evaluated with Student’s t test for differences in a paired design [8]. P < 0.05 was considered statistically significant.

RESULTS

The area of hyperalgesia surrounding the injury was not significantly altered by EMLA treatment compared with placebo (fig. 1A). The effect of EMLA was evaluated at all times (16 h, P = 0.68; 20 h, P = 0.37; 24 h, P = 0.14; and 48 h, P = 0.07; Wilcoxon test). The level of significance was reduced to 1 % in these comparisons with Bonferroni correction, because of the multiple comparisons. The area under the curve (AUC) for hyperalgesia was applied as a
summary measure of the total hyperalgesic response. AUC for secondary hyperalgesia after EMLA treatment was not significantly different from that after placebo (P = 0.18; Student’s paired t test, n = 12). 

The effect of EMLA on primary mechanical hyperalgesia (fig. 1 B) was analysed in the same way and there was no significant differences between EMLA and placebo (0 h, P = 0.20; 16 h, P = 0.28; 20 h, P = 0.29; 24 h, P = 1.00; and 48 h, P = 0.25; Wilcoxon test). Comparison of AUC values confirmed this finding (P = 0.19; Student’s paired t test).

Data for primary thermal hyperalgesia (fig. 1 C) and skin erythema index (fig. 1 D) were analysed with both AUC summaries and parametric two-way ANOVA for repeated measurements. There were no significant differences between EMLA and placebo with both methods (primary thermal hyperalgesia: AUC, P = 0.80 and ANOVA, P = 0.61; and ery

Figure 1 A: Secondary hyperalgesia, that is area of hyperalgesia to von Frey pinprick (175 mN) outside the injury, after burn injury in healthy volunteers treated with EMLA (−−−−) or placebo (——). Time 0 h = measurements before thermal injury. Values are medians. Comparison of AUC values revealed no significant difference between secondary hyperalgesia in EMLA- vs placebo-treated legs (P = 0.18; Student’s paired t test, n = 12). 

A: Secondary hyperalgesia, that is area of hyperalgesia to von Frey pinprick (175 mN) outside the injury, after burn injury in healthy volunteers treated with EMLA (−−−−) or placebo (——). Time 0 h = measurements before thermal injury. Values are medians. Comparison of AUC values revealed no significant difference between secondary hyperalgesia in EMLA- vs placebo-treated legs (P = 0.18; Student’s paired t test, n = 12). 

B: Primary mechanical hyperalgesia, that is mechanical pain detection threshold to von Frey pinprick, in the area of the burn injury. Values are medians. Comparison of AUC values revealed no significant difference between primary mechanical hyperalgesia in EMLA- (−−−−) vs placebo- (——) treated legs (P = 0.19; Student’s paired t test, n = 12). Von Frey hair no. (1–10) represents a rank scale, where 1 indicates a force of about 3 mN and 9 about 175 mN, whereas 10 indicates that 175 mN did not produce pain or discomfort. The steps from 1 to 9 are logarithmic increases in force (see text). 

C: Primary thermal hyperalgesia, that is heat pain detection threshold (HPDTS) in the area of the burn injury. Values are means. Comparison revealed no significant difference between primary thermal hyperalgesia in EMLA (−−−−) vs placebo (——)-treated legs (P = 0.61; parametric two-way analysis of variance for repeated measurements, n = 12). 

D: Skin erythema, that is the intensity of erythema inside the burn injury assessed with a hand-held skin reflectance spectrophotometer. Values are means. Comparison revealed no significant difference between erythema in EMLA (−−−−) vs placebo (——)-treated legs (P = 0.34; parametric two-way analysis of variance for repeated measurements, n = 12).

Table 1 Positive answers out of 12, in a questionnaire (yes/no) completed by the 12 subjects

<table>
<thead>
<tr>
<th>Changes in injury</th>
<th>Placebo (1 week)</th>
<th>EMLA (1 week)</th>
<th>Placebo (2 weeks)</th>
<th>EMLA (2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Irritated by touch</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Itch</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Any colour change</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Crusts</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Blister</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin erythema</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2 Minimum differences between treatments detectable with a power of 90 % (type II error of 10 %) and a type I error of 5 %. Differences are presented as the weighted mean for the observation period (AUC divided by 48 h)

<table>
<thead>
<tr>
<th>Secondary hyperalgesia (cm²)</th>
<th>Primary mechanical hyperalgesia (von Frey No.)</th>
<th>Primary thermal hyperalgesia (°C)</th>
<th>Erythema index (arb. unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>0.9</td>
<td>2.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Discussion

We examined if prolonged and intensive topical treatment with local anesthetics reduced late hyperalgesia, blister formation or erythema after thermal injury in healthy volunteers in a double-blind, randomized study. We found that the local anesthetics neither reduced local inflammation and late
hyperalgesia nor produced apparent changes in wound healing, although the sample size does not exclude minor differences. This result may seem surprising, considering the known anti-inflammatory effects of local anaesthetics. Several in vitro studies have demonstrated reduced production of free oxygen radicals from polymorphonuclear leucocytes after treatment with local anaesthetics [10–14], and reduced adherence and migration of leucocytes have been documented in different in vivo models [15–18]. Furthermore, local anaesthetics inhibit movement of leucocytes and phagocytosis in vitro [14, 19–21]. Local anaesthetics have also been shown to reduce albumin extravasation in rats after burn injury and chemical peritonitis [22, 23] and to modify the inflammatory response to experimental colitis [24] and irradiation [25].

Local anaesthetics may alter release of inflammatory mediators, for example histamine release from mast cells in vitro [26], leukotriene B-4 and interleukin-1 release from polymorphonuclear granulocytes and mononuclear cells in vitro, respectively [27]. The flare reaction induced by trauma and injection of inflammatory mediators is diminished by local anaesthetics, in contrast with the weal and local red reaction [28–30]. Thus local anaesthetics block axon reflexes and sensory functions of nociceptors. Inhibition of axon reflexes reduces local, indirect release of inflammatory neuropeptides, but the clinical importance of diminished neurogenic inflammation is unclear. It is not known if the local effector function of directly stimulated nociceptors is affected by local anaesthetics [31]. Furthermore, local anaesthetics have been shown to inhibit substance P receptor binding [32]. Thus several anti-inflammatory effects of local anaesthetics have been demonstrated in vitro and in animal models, but evidence of effects in human studies is, to our knowledge, restricted to one uncontrolled study and one case report, where lignocaine improved ulcerative proctitis and severe interstitial cystitis, respectively [33, 34]. Topical lignocaine has been tested several times in asthmatic subjects with conflicting, but mainly negative results [35–37]. Topical lignocaine had no effects on allergen-induced nasal secretion, blood flow or obstruction, in allergic individuals [38]. We have shown earlier that short-lived topical application, or subcutaneous infiltration with local anaesthetics, did not affect inflammation after burn [3]. This study, with prolonged and intensive treatment, supports this conclusion. Our findings, and the lack of other clinical evidence, may therefore question the relevance of the anti-inflammatory effects of local anaesthetics.

There may be different explanations for our results. First, the response involves several inflammatory mediators and cell types, which may not be affected by local anaesthetics. Second, the timing of the treatment (before compared with after injury) may be important in modulating inflammatory responses, as early mediators release cascades of secondary mediators. In this study we preferred treatment after injury, as this mimics most clinical situations, while treatment was initiated before injury in our first study [3]. Apparently, this did not affect the results. Third, the effects of prolonged topical treatment were either too transient or incapable of altering the course of the inflammatory response. Although the analgesic effects did not last into the observation period (16–48 h after injury), we do not question the effectiveness of EMLA cream in pain relief, but effects on hyperalgesia should not be expected for prolonged periods (more than 8 h) after removal of the cream. The potential reduction of leukotriene B-4, interleukin-1, histamine, free oxygen radicals and activated leucocytes by local anaesthetics [27] should attenuate sensitization of nociceptors in the injury, but removal of EMLA cream 8 h before the first measurements may have returned the process to its natural course. Fourth, we studied only 12 subjects and we may have missed some real differences. The minimal differences between treatments detectable in this study, with a power of 90 %, are shown in table 2.

The consequences for wound healing after treatment with local anaesthetics are controversial. The synthesis of collagen and glycosaminoglycans by fibroblasts in vitro is reduced by local anaesthetics [39], as is the tensile strength of skin wounds in rats [40]. Other studies [41], including our own, have been unable to demonstrate adverse clinical effects on host defences and wound healing, but our study is less specific in this respect than the first mentioned studies, and prolonged use of local anaesthetics may threaten tissue defences.

Acknowledgements

The study was supported by grants from the John and Birte Meyer Foundation, the P. A. Messerschmidt and Wife’s Fund, Fonden til Laegevidenksabens Fremme and Astra Pain Control, Södertälje, Sweden.

References


