A clinical study on two single unit dose packages (EMLA patch) and EMLA 5% cream used to reduce pain at IV cannulation in children

Study dates: Not available from original CSR, which predates ICH-E3 guidance. The study was terminated early due to problems with the adhesiveness of the patches.

Phase of development: Therapeutic confirmatory (III)

Principal Investigator: A Nilsson
Posta address not available from original CSR

Sponsor’s Responsible Medical Officer: Annette Rotstein, DDS, BSc
Astra Pain Control AB
S-15185 Södertälje
Sweden

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.
Study centre(s)

The study was conducted in 1 centre in Sweden.

Publications


Objectives and criteria for evaluation

Table S1 presents the objectives and outcome variables for this study.

Table S1       Primary and secondary objectives and outcome variables

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome variables</th>
<th>Type</th>
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<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>To compare 2 types of EMLA patches, 2 types of placebo patches, EMLA 5% cream in combination with Tegaderm™ and placebo cream in combination with Tegaderm™, regarding analgesic effect and local skin reactions when used to reduce pain from IV cannulation on the dorsum of the hand.</td>
<td>Subject assessment of pain from the cannulation on a 100 mm VAS, with endpoints as follows: no pain (0 mm) and the worst possible pain (100 mm) Investigator assessment of subject’s pain reaction on a 4-point verbal rating scale: no, slight, moderate, and severe.</td>
<td>Efficacy</td>
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<td>Presence of local sensations such as itching and burning, indicated by ‘yes’ or ‘no’. Presence of local skin reactions such as redness, pallor, and oedema using a 4-point verbal rating scale: no, slight, moderate, and severe.</td>
<td>Safety</td>
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<td><strong>Secondary</strong></td>
<td><strong>Secondary</strong></td>
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<td>To study the adhesiveness of the patches compared to the adhesiveness of Tegaderm used in combination with the cream.</td>
<td>Degree of adhesiveness of the patch/Tegaderm to the skin on a 4-point scale: 100% (totally affixed), ≥50%, &lt;50%, 0% (not affixed).</td>
<td>Efficacy</td>
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EMLA  Eutectic mixture of local anaesthetics; IV  Intravenous; VAS  Visual analogue scale.

Study design

The study was designed as a double-blind, placebo-controlled trial and partly as an open randomized trial in which subjects were randomized to receive either cream (EMLA [eutectic mixture of local anaesthetics] 5% cream or matching placebo) or patch (EMLA type I or type III or matching placebo patches) prior to IV cannulation. Half a tube of cream (2.5 gm used in combination with Tegaderm™) or a patch (type I or type III) was applied at least 60 minutes before cannulation to the dorsal side of one hand. After application, the adhesiveness of the patch/Tegaderm to the skin was recorded. After the stipulated application time, the cream or patch was removed, the subject was questioned about local skin sensations and the area was inspected for local skin reactions. The cannulation was then carried out. The subject and the investigator assessed the degree of pain after the cannulation procedure.
Target subject population and sample size

Male or female children, 7 to 15 years of age, who were scheduled for inpatient or outpatient surgery under general anaesthesia where an intravenous (IV) cannula was required were eligible for this study. Subjects with a known or suspected allergy to local anaesthetics of the amide type were ineligible to participate in this study. A total of 150 subjects were planned. Forty subjects in the active groups and 10 patients in the placebo groups were required to achieve 80% power to detect a mean difference of 20 mm on the VAS between each active treatment group and the combined placebo group. This calculation assumed a standard deviation of 20 mm and a significance level of 0.05.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Commercially available EMLA 5% cream was used in this study. This formulation consisted of lidocaine (25 mg [107 mmol/L]); prilocaine (25 mg [113 mmol/L]); Arlatone® 289 (19 mg); Carbopol® 934 (10 mg); and distilled water (up to 1 g [1 mL]). The total concentration of the active ingredients (lidocaine and prilocaine) was 50 mg/mL; Arlatone (emulsifier) and Carbopol (thickener) were used to obtain a suitable consistency. In the placebo cream, the eutectic mixture of the local anaesthetic bases was replaced by Miglyol® oil. Tegaderm 5 × 7 cm (3M, USA) was used as an occlusive dressing.

EMLA patch type I was a single-unit-dose package consisting of a macroporous membrane containing 1.2 g EMLA 5% cream. EMLA patch type III was a single-unit-dose consisting of a matrix saturated with 1 g EMLA 5% emulsion. EMLA contained a eutectic mixture of lidocaine and prilocaine, each at a concentration of 25 mg/mL. Foam medical tape (3M, USA) was used as adhesive.

Investigational products were administered topically to the dorsal side of one hand. The EMLA and placebo creams were visually and cosmetically identical and packed in identical 5 g tubes. The EMLA and placebo patches were also visually and cosmetically identical and packed in identical closure folds.

Duration of treatment

Subjects received a single application of investigational product at least 1 hour prior to undergoing IV cannulation.

Statistical methods

Differences in pain were to be analysed by using the Mann-Whitney U-test or, if the distribution of scores was approximately normal, by using a t test. Differences in frequency of local reactions were to be analysed by the chi-square test.

Subject population

The study aimed to enrolled 150 children; however, the trial was stopped when 50 subjects were enrolled due to problems with the adhesiveness of the 2 patches.
Of the 50 subjects included in the study, 40 subjects were in the active treatment groups (13 in EMLA cream group; 12 and 15 in the EMLA patch type I and type III groups, respectively) and 10 subjects were in the placebo groups (4 in the placebo cream group; 3 subjects each in the placebo patch type I and type III groups). Overall, subjects were equally distributed between male and female (50% each), and had a median age of 11 years (range: 7 to 15 years) and a median weight of 34 kg (range: 20 to 72 kg).

**Summary of efficacy results**

Problems with the adhesiveness of the patches caused early termination of the trial; thus data on patch adhesiveness was not provided in the study.

The analgesic effect of the treatment was not evaluated because of the small number of subjects.

**Summary of safety results**

During this study, no severe local skin reactions were observed.

Redness (slight) under the cream-covered area was observed in only 1 subject (EMLA patch type III group), whereas pallor (slight) was observed under the cream-covered area in 11 subjects in the active groups (4 in the EMLA cream group, 1 in the EMLA patch type I group, and 6 in the EMLA patch type III group) and 2 subjects in the placebo cream group. Redness (slight) under the adhesive-covered area was observed in 5 subjects (4 in the EMLA patch type III group and 1 in the placebo patch type III group). Oedema did not occur in any of the groups. One patient in the EMLA patch type III group felt a burning sensation on the skin. No other local skin reactions were observed.

**Conclusion(s)**

Because of the small number of subjects in this study due to early termination of the trial, the efficacy of EMLA patches was not evaluated. Local skin reactions were minor and transient.