Lidocaine 70mg/tetracaine 70mg medicated plaster (Rapydan®)

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Rapydan® is a medicated plaster containing lidocaine 70mg and tetracaine 70mg. It is licensed for anaesthesia of the skin prior to needle puncture in adults and superficial surgical procedures in adults.
- Two randomised controlled trials (RCTs) in adults have shown it to be superior to placebo for local anaesthesia prior to painful dermatological procedures and vascular access procedures.
- Use of the plaster prior to minor dermatological procedures in adults over 65 years of age produced less favourable results than the other trials conducted in adults.
- An RCT investigating the use of the plaster in children prior to vascular access procedures showed it was superior to placebo.
- No published trials have included an active comparator.
- The most common adverse effects are erythema, oedema and blanching. Other adverse reactions reported include abnormal sensation, rash and contact dermatitis.
- The manufacturers advise that the lidocaine/tetracaine plaster is effective after 30 minutes, which is a shorter time than that advised by the manufacturers of lidocaine/prilocaine cream (EMLA®) for the same indication (60 minutes). It is licensed for more indications than tetracaine gel (Ametop®).
- The plaster is more expensive than the other topical preparations available for surface anaesthesia.

Introduction

Topical anaesthetics are commonly used to provide local analgesia prior to venepuncture or other dermatological procedures. This is because many patients are afraid of needles or the brief pain caused by an injection with local anaesthetic.1,2 The lidocaine/tetracaine plaster (Rapydan®) is a new product available for local anaesthesia, designed as an alternative to other topical preparations such as creams or gels. Rapydan® uses a patented controlled heat-assisted drug delivery (CHADD™) system to aid the delivery of a eutectic mixture of lidocaine and tetracaine.1 The CHADD™ heating component is activated by exposure to oxygen when the patch is removed from its airtight storage pouch.3

Evidence

Four randomised, double-blind, placebo-controlled trials have been published for the lidocaine/tetracaine medicated plaster.2,4,5,6 Three of these trials studied the use of the plaster in adults, one included only adults over 65 years of age, and one specifically looked at the use of the plaster in children. All were similar in terms of exclusion criteria and outcome measures.

No published trials have included an active comparator. All trials are limited by the fact that pain is very subjective and therefore difficult to measure objectively.

The largest published trial investigated the use of the lidocaine/tetracaine medicated plaster in adults prior to painful dermatologic procedures such as superficial excision and shave biopsy.4 In this study, 94 patients were randomised to receive a 30 minute administration of either the active or placebo patch immediately before their procedure. Patients rated their pain using the visual analog scale.
Lidocaine/tetracaine topical patch (Rapydan®)

(VAS) where 0mm indicates no pain and 100mm indicates worst possible pain. The median VAS scores were 5mm for the active patch and 31mm for the placebo patch (p<0.001). No mean VAS scores or interquartile ranges were published. Other outcome measures in this study including the investigator and independent observer’s ratings of pain also favoured the lidocaine/tetracaine plaster over placebo.

The second trial in adults over 18 years looked at the efficacy of the lidocaine/tetracaine medicated plaster prior to vascular access procedures. In this trial volunteers were given both an active and placebo patch, one on each antecubital surface, with the active patch being randomised between the left and right arm, so they acted as their own control. A vascular access procedure was then performed on first the right then the left antecubital surface. Patients rated their pain using the VAS immediately after each vascular access procedure. The median subject VAS score was 5mm for the active patch and 28mm for placebo and 49% of subjects had lower VAS scores with active patch than placebo, although 17% had lower VAS scores with placebo. Secondary outcome measures, including the investigator and independent observer’s ratings of pain, also favoured the lidocaine/tetracaine plaster over placebo.

Use of the lidocaine/tetracaine plaster prior to minor dermatological procedures in adults over 65 years produced less favourable results than the other trials conducted in adults. Patients were randomised to either active or placebo patch and asked to rate the amount of pain experienced using the VAS. The median VAS score was significantly lower for the active patch than placebo (9.5mm vs. 22.5mm; p=0.041) but the graph displaying the range of results with the active and placebo patches suggests that the mean of the VAS scores would be less favourable towards the active patch. Subgroup analysis shows that median VAS scores were only statistically significant for patients who underwent superficial excisions or procedures performed on the head and neck. Differences between the active and placebo groups were not statistically significant for shave biopsies or procedures performed on other parts of the body. Other outcome measures did not show a statistically significant difference between the active and placebo groups.

The randomised controlled trial examining the use of the lidocaine/tetracaine medicated plaster in children favoured the active patch over placebo. Patients in the active patch group reported significantly lower pain with the vascular access procedure compared to those in the placebo group: median Oucher scores of 0 vs. 60; p < 0.001, 25th to 75th interquartile ranges 0-35 vs. 20-80. Investigator and independent observer evaluations reported no pain during vascular access procedures in 31 patients (76%) in the active patch group, compared to 3 or 4 (15 to 20%) patients in the placebo group.

Safety

The most common adverse drug reactions with the use of the lidocaine/tetracaine medicated plaster are erythema, oedema and blanching, occurring in 71%, 12% and 12% of patients respectively. Other adverse reactions reported include abnormal sensation, rash (≥1 in 100 to <1 in 10), contact dermatitis (≥1 in 1,000 to <1 in 100) and skin discoloration (≥1 in 10,000 to <1 in 1,000). Allergic or anaphylactoid reactions may occur with lidocaine, tetracaine or other components of the medicated plaster.

Patients should be monitored for possible pain. The median VAS score was 5mm for the active patch and 31mm for the placebo.

NHS Impact

Lidocaine 2.5%/prilocaine 2.5% cream (EMLA®) and tetracaine 4% gel (Ametop®) are the current treatment options for local anaesthesia of the skin. They are licensed for use in a wider age range than the lidocaine/tetracaine medicated plaster.

The lidocaine/tetracaine medicated plaster and lidocaine/prilocaine cream may be used for surface anaesthesia of the skin prior to any minor superficial dermatological procedure, but tetracaine gel is only licensed for use prior to venepuncture or venous cannulation. Lidocaine/prilocaine cream must be applied to the skin for at least 60 minutes before a minor dermatological procedure, whereas the lidocaine/tetracaine plaster only needs to be applied for 30 minutes. Tetracaine gel is also effective after 30 minutes for venepuncture, but requires 45 minutes to anaesthetise the skin prior to venous cannulation.

Appendix I: Table of Clinical Trials

Risk Management Issues:

Patches must not be cut and should not be used if the patch has been damaged in any way because excessive exposure to the air could cause the patch to overheat due to increased activation of the CHADD™ by oxygen.

The lidocaine/tetracaine medicated plaster contains a heat-releasing component that may reach a maximum temperature of up to 40°C.

After use the patch should be folded together with the adhesive mass inwards, and for safety and environmental reasons returned to the pharmacy for disposal.
References


Key papers are highlighted in bold.
### Appendix I

#### Table 1. Clinical Trials of Lidocaine/tetracaine topical patch

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<td>Ref 2</td>
<td>Randomised, double-blind, placebo-controlled trial conducted at two medical centres; 20 subjects at each centre. Subjects given both an active and placebo patch, with treatment sites randomised between the right and left antecubital surfaces. Vascular access procedure was performed first on the right antecubital surface, then the left.</td>
<td>Adults over 18 years. Exclusion criteria • Known allergy or sensitivity to lidocaine, tetracaine or other local anaesthetics or any component of the test materials. • Taken any prescription strength analgesic medication in the previous 24 hour period. • Damaged, denuded or broken skin at designated patch site. • Pregnancy or breastfeeding.</td>
<td>Adverse events: 1 report of itching at the patch application site and 1 report of itching and erythema after patch removal. <strong>Primary Outcome</strong> Patient report of pain intensity using a 100mm visual analogue scale (VAS) where 0mm = no pain to 100mm = worst pain imaginable. <strong>Secondary Outcomes</strong> Yes or no question to subjects: ‘Did the local anaesthetic provide adequate pain relief for the vascular access procedure?’</td>
<td><strong>Primary Outcome</strong> Median subject VAS score was lower for active patch compared to placebo: 5mm vs. 28mm. 49% of subjects had lower VAS score with active patch and 17% of subjects had lower VAS score with placebo patch (P&lt;0.001). <strong>Secondary Outcomes</strong> More subjects reported adequate anaesthesia following the active patch than placebo: 73% vs. 31%. 59% of subjects indicated adequate pain relief with the active patch but not with placebo; 15% reported adequate pain relief with placebo but not the active patch (P=0.002). Investigators rated 63% of subjects as having no pain with active patch compared to 33% with placebo. Investigators considered 46% subjects to have less pain with active patch than placebo, and 15% to have less pain with placebo than active patch (P=0.021). Independent observers rated 68% of subjects as having no pain with active patch compared to 38% with placebo. They considered 46% of subjects to have less pain with the active patch than placebo, and 15% to have less pain with placebo than active patch (P=0.015).</td>
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<td>Ref 4</td>
<td>Prospectively randomised, placebo-controlled, double-blind trial. 94 patients over three separate study sites. Active patch or placebo used prior to minor dermatologic procedure. Adults. Exclusion criteria  - Known allergy or sensitivity to lidocaine, tetracaine or other local anaesthetics or any component of the test materials.  - Taken any prescription strength analgesic medication in the previous 24 hour period.  - Known sensitivity to sympathomimetic amines.  - Damaged, denuded or broken skin at treatment site.  - Pregnancy or breastfeeding.</td>
<td>n=45 for active patch; n=49 for placebo patch. Adverse events: 1 report of burning sensation at the patch application site. Patients in the active patch group experienced slightly more erythema and oedema than patients in placebo group, but this was not statistically significant.</td>
<td>Patient’s rating of pain intensity using the visual analogue scale (VAS). Patient’s overall assessment of the effectiveness of the patch. Need for rescue lidocaine injection during minor dermatological procedure. Investigator ratings of patient’s pain intensity and adequacy of the anaesthetic. Independent observer’s score of perception of pain intensity using post-procedure pain assessment scale.</td>
<td>Median VAS score was 5mm for the active patch group compared with 31mm for the placebo group (p&lt;0.001). 69% of patients who received the active patch rated their pain intensity as a score of less than 10 on the 0 to 100 VAS scale, compared to 24% of patients who received placebo. 73% of patients who received the active patch reported adequate anaesthesia compared to 37% of patients with the placebo patch. Injected lidocaine rescue was administered to 22% of the patients in the active treatment group, compared with 49% of the patients in the placebo group. The investigator rated 51% of patients who received the active patch as not having pain during the procedure, compared with 10% of patients with the placebo patch (p&lt;0.004). The independent witness rated 53% of patients who received the active patch as not having pain during the procedure, compared with 10% of patients with the placebo patch (p&lt;0.001).</td>
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<td>Ref 5</td>
<td>Randomised, double-blind, placebo-controlled study of patients presenting to study site for minor dermatological procedure.</td>
<td>Males or females who were 65 years of age or older. Exclusion criteria: • Known sensitivity to sympathomimetic amines. • Known sensitivity to any of the active or inactive ingredients in the active or placebo patch. • Damaged, denuded or broken skin at the designated patch site. • Use of prescription-strength analgesic medication during the 24-hour period prior to the procedure.</td>
<td>n= 79 at entry n= 74 at efficacy analysis Adverse events: 22% patients in the active group developed erythema at the application site, vs. 16% in placebo group. Oedema was noted in 6 patients in the active group compared to 0 patients in the placebo group.</td>
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**Primary Outcome**

Patient report of pain experienced during procedure using a 100mm visual analogue scale (VAS) where 0mm = no pain to 100mm = worst pain imaginable.

**Secondary Outcomes**

- Patient’s assessment of whether the patch provided adequate anaesthesia for the procedure (yes/no).
- Whether the patient would use the patch again to provide anaesthesia for a similar procedure (yes/no).
- Investigator’s assessment of the degree of anaesthesia provided by the study patch (no pain, slight pain, moderate pain, severe pain).
- Investigator’s assessment of whether the study patch provided adequate anaesthesia for the procedure (yes/no).
- Independent observer’s assessment of the degree of anaesthesia provided by the study patch (no pain, slight pain, moderate pain, severe pain).

**Results**

Lower patient rating of pain in the active patch group compared with the placebo group: median score 9.5mm vs. 22.5mm (p=0.041).

No statistically significant difference between active and placebo groups for the percentage of patients reporting adequate pain relief (p=0.767) or percentage of patients who indicated that they would use the study patch again for anaesthesia (p=0.726).

No differences between the active and placebo groups for the investigator's assessments of patient pain (p=0.696), the independent observer’s assessments of patient pain (p=0.416) or the investigator’s impression of whether the local anaesthetic provided adequate anaesthesia (p=0.838).
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| Ref 6  | Randomised, double-blind, placebo-controlled trial conducted at two separate sites. | Children aged 3 to 17 years old. | Exclusion criteria  
  - Known sensitivity to components of the test materials.  
  - Damaged skin at the designated patch site.  
  - Pregnancy or breastfeeding.  
  - Allergic skin hypersensitivity or allergy to amide or ester local anaesthetics.  
  - Use of analgesics during the past 24 hours.  
  - Inability to understand or use the pain assessment tool.  
  n= 43 at entry and n= 41 at efficacy analysis for active patch; n= 21 at entry and n= 20 at efficacy analysis for placebo patch.  
 | Primary Outcome  
 Pain intensity as determined by the Oucher pain scale (a vertical six-photograph scale with a corresponding vertical numerical scale of 0-100 marked off in units of 10 points; 0 score indicates no pain and 100 points indicates worst possible pain).  
 Patients who received the active patch had slightly more erythema and oedema than patients who received placebo, but the difference was not statistically significant.  
 | Patients in the active patch group reported significantly lower pain associated with vascular access procedure than with the placebo group: median Oucher scores of 0 vs. 60; p<0.001 and 25th to 75th interquartile ranges of 0-35 vs. 20-80 respectively.  
 24 patients (59%) reported no pain in the active patch group vs. 4 patients (20%) in the placebo group.  
 2 patients (5%) in the active patch group reported severe pain vs. 4 patients (20%) in the placebo group. |
|        |              |                  |                                   | Secondary Outcome  
 Investigator and independent observer separately evaluated the degree of analgesia provided by the study drug by completing a four-point categorical scale (no pain, slight pain, moderate pain, severe pain).  
 | Investigator and independent observer evaluations reported no pain during vascular access procedures in 31 patients (76%) in the active patch group, compared to 3 or 4 (15 to 20%) patients in the placebo group. |