Novel bioadhesive delivery system for percutaneous local anaesthesia

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We have assessed the efficacy of a novel bioadhesive amethocaine patch device, compared to Ametop™ gel, in a randomized, double-blinded trial. Patch and gel formulations, including placebos, were applied to the forearms of volunteers (n=30) for 40 min. Once the formulations were removed from the skin, anaesthesia was assessed by volunteers using a conventional pin-prick test. Pain scores were recorded for 4 h after removal of gels and patches. Statistical analysis of the results indicated that both amethocaine gel and patch preparations were superior to placebo (P<0.05). No significant difference was observed between amethocaine gel and patch formulations (P>0.05) in either onset time or duration of action for percutaneous local anaesthesia. The results of this study indicate therefore that the novel bioadhesive patch provides clinically comparable anaesthesia to the established gel formulation in a more defined dosage form.

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There are two products available in the UK for provision of topical anaesthesia, EMLA® cream and Ametop™ gel. The former is based on a eutectic mixture of the amide local anaesthetics lidocaine and prilocaine (2.5% w/w of each anaesthetic), while Ametop™ contains 4% w/w amethocaine in a hydrophilic gel. Several clinical studies have recently compared the efficacy of EMLA® and Ametop™, indicating that Ametop™ gel provides a more rapid onset time and a greater duration of anaesthesia than EMLA® cream.1-4 This has been attributed to the use of the amethocaine phase-change system by Ametop™ gel.

In this system, the water in the gel forms a meta-stable hydrate with amethocaine and lowers the melting point of the drug from 42°C to ~30°C.5,6 Therefore, when Ametop™ gel is applied to intact skin a phase change occurs whereby solid particles of amethocaine convert into highly penetrative oil globules.

Although gel systems are relatively simple to manufacture and use, they can be inconvenient in certain situations, for example, where the mass of gel to be applied is large or where a specific region on the skin such as a port-wine stain needs to be treated accurately.7 The formulation and clinical assessment of a hydrophilic amethocaine-containing patch device for percutaneous local anaesthesia has been previously described.8 The patch device described produced comparable skin anaesthesia to amethocaine gel formulations. However, the film was non-adhesive and was secured to the skin by means of a pressure-sensitive island dressing, which was complex in design and difficult to make.

The formulation and characterization of an integrated, moisture-activated, bioadhesive amethocaine patch for percutaneous local anaesthesia has been recently reported.9 While this device also employs the amethocaine phase-change system, it does not require further surrounding adhesive dressings, as it is formulated to incorporate a bioadhesive co-polymer.5 This device is relatively simple to make and the patch has the advantage of being removed easily from skin by peeling without leaving a residue.

The amethocaine phase-change system has to date provided the most clinically successful method for delivery of percutaneous local anaesthesia. Therefore, the aim of this study was to evaluate, in a randomized, double-blinded cross-over study, the clinical effectiveness of an integrated, water-activated bioadhesive patch device based on the amethocaine phase-change system by comparing it with the established Ametop™ gel.5

Materials and methods

Biodhesive amethocaine patches were prepared from gels containing 1% w/w amethocaine, as described previously.9 Placebo patches were similarly prepared. Both patches
were presented in heat-sealed pouches. Ametop\textsuperscript{TM} gel was supplied by Smith & Nephew. A placebo gel was also prepared to match the active formulation. Both gels were packaged into standard lacquered aluminium tubes, using conventional pharmaceutical methods.

Upon obtaining Ethical Committee approval, 30 volunteers (16 female, 20–22 yr) were recruited for the trial. All volunteers completed the study.

Double-blinding of the study was carried out by randomly allocating each formulation a code. Gels (1 g containing amethocaine 40 mg and placebo gel) and patches (3 × 3 cm, containing amethocaine 40.5 mg and placebo patch) were applied to the ventral surface of the forearm; gels (covering an area of 9 cm\textsuperscript{2}) were covered with a standard dressing. Patches were moistened for 10 s and then placed upon the ventral surface of the forearm of the volunteer whereupon a bioadhesive bond was formed. All volunteers received each of the four formulations (active gel and patch, placebo gel and patch) on four separate occasions. A period of 7 days was observed between administration of formulations. Each formulation was left on the forearm for 40 min. The formulation was then removed and the treated site wiped clean. The volunteers were instructed to prick the site six times, using a sterile Microlance 25G5/8, in a random fashion\textsuperscript{10, 11} and, thereafter, the evoked pain was recorded on a four-point scale (1 = no pain; 2 = slight sensation; 3 = moderate pain; 4 = no apparent anaesthesia). Pain scores were assessed by each volunteer, at the specified time periods, after patch or gel removal. Pain scores were recorded and the mean score at each time period was determined. Volunteers were also encouraged to comment upon any aspect of the dosage form or the trial they desired.

Data from each volunteer were collated after the trial and analysed by application of a two-way analysis of variance (ANOVA) with repeated measures. Further analysis was carried out by performing a Fisher exact test for the mean. A significance level of 5\% was chosen in all tests.\textsuperscript{8, 9}

Pain scores obtained for Ametop\textsuperscript{TM} gel and the amethocaine patch, at each time point, were compared statistically using the chi-square method with a 2 \times 2 contingency table and employing a continuity correction.

Power was estimated using an approximate two-sample t-test, using the means and standard deviations for the gel and bioadhesive patch at each time point. Overall, the power was estimated at \approx 90\% to detect a difference of 1 in the pain scores.

### Results

Analysis of variance showed that there was a significant difference between the formulations ($P<0.05$). This was determined, upon further analysis, to be because of the inclusion of the placebo preparations. Analysis of the combined pain scores throughout the duration of the self-assessment period showed that with Ametop\textsuperscript{TM} gel 84.4\% of the volunteers had a pain score of 1, compared with 80.3\% of those with a bioadhesive amethocaine patch. Both placebos yielded the maximum pain score of 4. Statistical analysis using the Fisher exact test indicated that there was no significant difference between the placebo gel and patch formulations over the entire time period of the study ($P>0.05$). There was a significant difference ($P<0.05$) between placebo and active formulations. There was no significant difference ($P>0.05$) between the amethocaine gel and patch formulations. Table 1 illustrates the distribution of pain scores 1 and 2 for Ametop\textsuperscript{TM} gel and the amethocaine patch (there were no reported pain scores of 3 or 4, for either active formulation, during the course of the study).

Statistical analyses of the pain scores obtained at each time point indicated that there was no significant difference ($P>0.5$) between Ametop\textsuperscript{TM} gel and the amethocaine patch.

### Discussion

There are a number of potential advantages in designing a bioadhesive patch device for providing percutaneous local anaesthesia. Each patch will have a specific amount of drug applied to a clearly defined area; this is not possible when using gels or creams. Furthermore, application and removal of the device are potentially easier as gels and creams require a covering to protect them from removal from the skin surface. This covering needs to be removed prior to wiping such formulations from the surface of the skin. Removal of the covering, normally a pressure-sensitive adhesive dressing, can also be quite a painful procedure. Although a previous amethocaine patch device has been described, it was not bioadhesive and required a dressing to maintain skin contact.

The results of the study clearly demonstrated the differences between active and placebo formulations. The mean pain scores for both Ametop\textsuperscript{TM} gel and the amethocaine patch were less than 2 throughout the assessment period, and statistical analyses of the results indicated that there was no difference in the active preparations. Interestingly, pain scores of 3 and 4 were not reported at any time point.
and this is in broad agreement with earlier reports on amethocaine-based systems.

The recommended application time for Ametop™ gel is between 30 and 45 min, with the shorter application time being used for children. It has been previously reported that pain scores of either 1 or 2 are classified as clinically effective, and hence both active formulations provided satisfactory percutaneous local anaesthesia.\(^8\) The distribution of pain scores 1 and 2 clearly illustrated that as time progressed the number of pain scores of 1 gradually increased to the point where all volunteers gave this result; this occurred from ~60 to 150 min. It was also observed that pain scores continued to decrease even after removal of the active preparations. This is due to a drug reservoir being present in the stratum corneum so that drug diffusion into underlying tissues continues after removal of the active formulations.\(^8\) After 150 min the number of pain scores of 1 began to decrease while pain scores of 2 increased. Nevertheless, from a clinical viewpoint there was satisfactory percutaneous local anaesthesia in all of the volunteers over the entire period of the study (240 min).

In a recent study,\(^12\) a liposome-encapsulated amethocaine formulation was applied to 40 volunteers for a period of 1 h and anaesthesia was monitored by pin prick. Although volunteers reported a good anaesthetic effect, the formulation failed to provide percutaneous local anaesthesia in 5% of the subjects. Hence, it was suggested that certain individuals may require longer application times. This, perhaps, is not surprising given that the drug must first be released from the liposome before it can produce percutaneous local anaesthesia.

In the present study, no significant side effects were evident. Three volunteers reported slight, transient erythema at the site of application with the amethocaine patch, and two other volunteers reported a similar reaction after application of the amethocaine gel. These findings are in good agreement with the incidence of such reactions in other studies. However, in a recent report\(^12\) concerning percutaneous local anaesthesia using liposome-encapsulated amethocaine, it was stated that 80% of the volunteers exhibited erythema. A possible explanation for this was that a higher concentration of drug was used (5%) and the application time was 1 h. The results of this study indicate that the water-activated amethocaine patch device produces equivalent anaesthesia to the amethocaine aqueous gel formulation. Therefore, the patch device tested in this study provided a suitable alternative to established gel or cream formulations. In addition, it delivers a specific amount of drug to a specific surface area of skin.

References
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