

CLINICAL PRACTICE

**Heated lidocaine/tetracaine patch (Synera™, Rapydan™) compared with lidocaine/prilocaine cream (EMLA®) for topical anaesthesia before vascular access**

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**Background.** We compared the lidocaine/tetracaine patch [Synera™ (USA), Rapydan™ (Europe)], a novel heat-aided patch using a eutectic mixture of lidocaine 70 mg and tetracaine 70 mg, with a eutectic mixture of lidocaine 25 mg ml<sup>-1</sup> and prilocaine 25 mg ml<sup>-1</sup> (EMLA® Cream). The agents were administered at different time periods for local topical anaesthesia before a vascular access procedure.

**Methods.** In this double-blind, paired study, 82 adult volunteers were randomized to receive the lidocaine/tetracaine patch on one antecubital surface and lidocaine/prilocaine cream on the other concurrently for 10, 20, 30, or 60 min before a vascular access procedure. Subjects rated pain intensity using a 100 mm visual analogue scale (VAS). Skin reactions and adverse events were also evaluated.

**Results.** Median VAS scores were significantly lower for the lidocaine/tetracaine patch than for lidocaine/prilocaine cream in the 10 min ( $P=0.010$ ), 20 min ( $P=0.042$ ), and 30 min ( $P=0.001$ ) application groups. The lidocaine/tetracaine patch was associated with significantly more erythema than lidocaine/prilocaine cream at 20, 30, and 60 min, whereas lidocaine/prilocaine cream produced more blanching than the lidocaine/tetracaine patch at 30 and 60 min. Two subjects reported nausea and faintness associated with the vascular access procedure; one was withdrawn from the study.

**Conclusions.** The lidocaine/tetracaine patch provided effective anaesthesia with an application time as short as 10 min and was better than lidocaine/prilocaine cream at all application times shorter than 60 min, demonstrating a substantial improvement in time to onset of anaesthesia. The lidocaine/tetracaine patch provided an important alternative to lidocaine/prilocaine cream for topical local anaesthesia.

*Br J Anaesth* 2009; **102**: 210–15

**Keywords:** anaesthetics local, lidocaine; anaesthetics local, prilocaine; anaesthetics local, tetracaine; pain; venepuncture

Accepted for publication: November 4, 2008

Many clinical procedures, including venepuncture, arterial puncture, lumbar puncture, percutaneous venous catheter placement, and dermatological procedures, may be

associated with pain or discomfort. Consequently, the procedural pain and associated stress and anxiety involved for some patients represent a significant clinical concern,

†*Declaration of interest.* J.S. has received honoraria for work conducted on behalf of ZARS Pharma. S.M. owns shares of ZARS Pharma. M.A.A. is a co-founder of ZARS Pharma, the sponsor of the clinical trial on which this paper is based. He also holds shares in ZARS Pharma and, during the conduct of the study, was an employee of ZARS. His role was to design the trial and act as a medical monitor. J.C.C. is an employee of Endo Pharmaceuticals.

which is often addressed by the use of topical anaesthesia. But, intact skin presents a significant barrier to available topical anaesthetic preparations. This means that many topical anaesthetic preparations must be applied at least 45–60 min before the clinical procedure to achieve the desired level of anaesthesia. In addition, current creams or gel-based preparations may require the use of occlusive dressings, adding to the time required for their application.<sup>1,2</sup> These factors place an additional burden on clinical staff and can lead to delays in administering the planned procedure.

The lidocaine/tetracaine patch (lidocaine 70 mg/tetracaine 70 mg, Synera™, known in Europe as Rapydan™) is a novel drug delivery system designed to warm the skin and enhance the delivery of local anaesthetics through the skin.<sup>3–5</sup> EMLA® Cream, a widely used topical anaesthetic, is a eutectic mixture of lidocaine 25 mg ml<sup>-1</sup> and prilocaine 25 mg ml<sup>-1</sup>.<sup>6</sup> The objective of this study was to compare the efficacy and tolerability of the lidocaine/tetracaine patch with lidocaine/prilocaine cream when applied within 1 h of conducting vascular access procedures in adult volunteers.

## Methods

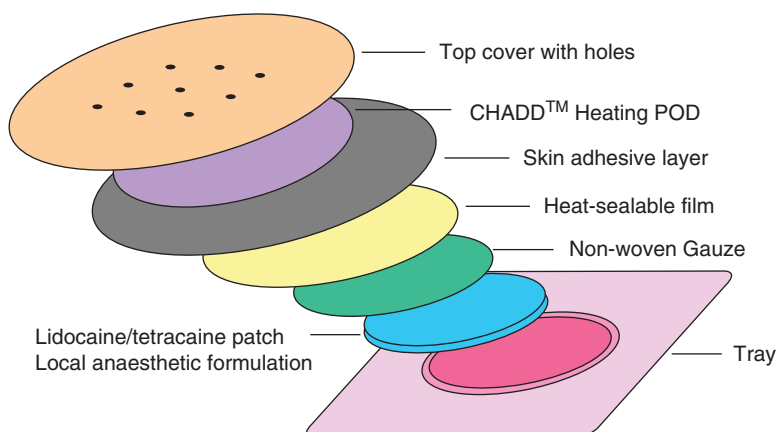
This randomized, double-blind, paired study compared the effectiveness of the lidocaine/tetracaine patch with that of lidocaine/prilocaine cream when administered for 10, 20, 30, and 60 min periods to provide dermal anaesthesia for vascular access procedures in adult volunteers. The study received approval from the Bro Taf Local Research Ethics Committee, Glamorgan, Wales, UK, and all subjects gave written informed consent before participation.

Eligible subjects were adults 18 yr of age or older of any race and gender who did not meet any of the following exclusion criteria: known allergies or sensitivities to lidocaine, tetracaine, prilocaine, or other local anaesthetic; known sensitivity to any components of the test materials (e.g. sulphites and adhesives); damaged, denuded, or

broken skin at the designated patch site; pregnant or breastfeeding; concomitant use of a prescription-strength analgesic within the previous 24 h; or previous use of lidocaine/prilocaine cream.

Subjects received concurrent applications of the lidocaine/tetracaine patch (ZARS Pharma, Salt Lake City, UT, USA) (Fig. 1) and lidocaine/prilocaine cream (AstraZeneca Pharmaceuticals, Macclesfield, UK). The lidocaine/tetracaine patch was activated by removing the patch from its air-tight pouch, peeling the release liner, and applying it to the skin. Lidocaine/prilocaine cream was applied under occlusion, according to the product's instructions for use.<sup>7</sup>

Eligible subjects were randomized into one of the four groups, according to the duration of time the treatment was to be applied: 10, 20, 30, or 60 min. Within each treatment group, subjects received a lidocaine/tetracaine patch on one antecubital surface and lidocaine/prilocaine cream concurrently on the other. Individual treatments were applied to the left or right arms according to a random scheme, by a study nurse who took no part in the study evaluations. Lidocaine/prilocaine cream was applied using an oval plastic template similar in size to the lidocaine/tetracaine patch so that the investigator could not determine treatment allocation. The study nurse then removed the study treatments before treatment evaluations. Immediately after removal of the treatments, the investigator, who remained blinded to the study drug applied to each arm, evaluated the treatment sites for skin reactions. After skin evaluation, the investigator performed a venepuncture of each right and left antecubital vein using a standard 18 gauge angiocatheter. In all cases, the procedure was performed on the right arm first. The investigator obtained a flash of blood to confirm that venous access was achieved. Once the flash was obtained, the angiocatheter was removed and the blood was discarded. After each procedure, the subject and investigator completed study evaluations. Before leaving the study site, subjects were asked to call the study site if a skin reaction developed.



**Fig 1** Diagram of the heated lidocaine/tetracaine patch.

The primary efficacy endpoint was subject report of pain intensity using a 100 mm visual analogue scale (VAS).<sup>8–9</sup> Secondary efficacy endpoints included: (i) subject evaluation of the effectiveness of the study drugs (whether the treatment provided adequate pain relief and whether the subject would be prepared to use the treatment again); (ii) investigator evaluation of the subject's pain intensity using a four-point categorical scale (0, no pain, through 3, severe pain); and (iii) investigator's overall impression of the study drugs (whether the study drugs provided adequate analgesia).

Safety and tolerability were evaluated based on the frequency of adverse events (AEs) and on evaluation of skin reactions after removal of each study drug. Five-point categorical scales were used to evaluate erythema (no erythema through severe erythema to slight eschar formation), oedema (no oedema through severe oedema), and blanching (no blanching through extreme blanching).<sup>10</sup>

One-way analysis of variance (ANOVA) was used to compare age of randomized treatment groups. Sex comparability was assessed by  $\chi^2$  analysis, and skin type comparability was evaluated using a Kruskal–Wallis test. Procedure duration was analysed using repeated-measures ANOVA, with the grouping factor of application time and the repeated measure of treatment type. Vascular access difficulty was compared between treatments using sign tests. Differences among application times between the lidocaine/tetracaine patch and lidocaine/prilocaine cream outcomes were expected, so the study was powered to analyse application time groups separately for these variables. Assuming a paired standard deviation of 15 units, a sample size of 20 subjects was determined to be sufficient to detect a difference of 10 units on VAS, with a power of 80% and a two-sided significance level of 5%. Consequently, the study was designed to include 20 subjects in each application time group. Subject VAS scores and investigator pain ratings were compared between treatments for each application time using the Wilcoxon signed-rank tests. Subject and investigator assessments of the elimination of pain and

subject's preparedness to use the study treatments again were compared between treatments using the McNemar tests for each application time. Exploratory comparisons of lidocaine/tetracaine patch VAS scores by application time were performed using the pairwise Mann–Whitney tests. Erythema and blanching were compared between treatments for each application time using the Wilcoxon signed-rank tests, and oedema was compared using sign tests.

## Results

A total of 82 subjects (37 males and 45 females) entered the study and were randomized. All subjects received both treatments; two subjects who were randomized to the 30 min treatment group inadvertently received each treatment for only 20 min and were included in the 30 min group for the analyses. All but one subject completed the study. This subject received the 10 min treatment and became nauseous and light-headed after the first vascular access procedure. The subject refused the second vascular access procedure and was withdrawn from the study.

The treatment groups were well matched in terms of age and sex (Table 1), with similar numbers of males and females in each group, except for the 60 min application arm (seven males and 13 females). Skin types (Table 1) also reflected a successful randomization process. There were no statistically significant differences for any patient characteristic variable among the different application time groups.

The mean duration of the vascular access procedure for each treatment group was ~6 or 7 s. There was no statistically significant difference in mean procedure duration between lidocaine/tetracaine and lidocaine/prilocaine treatments ( $P=0.267$ ). Most vascular access procedures (95%) were successful at the first attempt.

Median VAS scores were significantly lower for patients receiving the lidocaine/tetracaine patch compared with those receiving lidocaine/prilocaine cream for all treatment

**Table 1** Patient characteristics and skin type variables in different treatment groups; the groups were similar

Characteristics	Treatment group			
	10 min (n=20)	20 min (n=20)	30 min (n=22)	60 min (n=20)
Sex ( $P=0.226$ ) (n)				
Male	11	10	9	7
Female	9	10	13	13
Age (yr) ( $P=0.332$ )				
Mean (sd)	34.5 (10.2)	37.0 (12.5)	35.4 (11.3)	42.2 (16.2)
Range	23–56	20–57	18–61	18–72
Skin type ( $P=0.776$ ) (n)				
Always burns easily, rarely tans	3	3	3	4
Always burns easily, tans minimally	1	3	6	2
Burns moderately, tans gradually	6	7	4	7
Burns minimally, always tans well	6	5	7	5
Rarely burns, tans profoundly	3	2	2	2
Never burns, deeply pigmented	1	0	0	0

durations <60 min: 10 min (16 vs 33;  $P=0.010$ ), 20 min (15 vs 22,  $P=0.042$ ), and 30 min (2 vs 13;  $P=0.001$ ), respectively (Fig. 2). Median VAS scores were the same for lidocaine/tetracaine patch and lidocaine/prilocaine cream at 60 min (2 vs 2;  $P=0.887$ ) (Fig. 2).

Overall subject evaluations of the study treatments (Table 2) were consistent with the primary endpoint, indicating superior analgesia with the lidocaine/tetracaine patch after short treatment durations. Significantly more subjects in the 10, 20, and 30 min groups said they would use the lidocaine/tetracaine patch again compared with lidocaine/prilocaine cream. When considering the proportion of subjects who reported no pain associated with the vascular access procedure, significantly more subjects in the 20 and 30 min groups reported that the lidocaine/tetracaine patch eliminated pain compared with lidocaine/prilocaine cream ( $P=0.014$  and  $0.020$ , respectively). After the 10 min application of the lidocaine/tetracaine patch, 65% of subjects reported no pain, but the difference vs lidocaine/prilocaine cream did not reach statistical significance ( $P=0.059$ ). There was no difference between treatments in the 60 min group.

Investigator ratings of subject pain intensity were significantly lower for lidocaine/tetracaine patch applications in the 10 min group ( $P=0.046$ ). The pain intensity ratings for the remaining groups and the investigator's evaluation of the general effectiveness of the treatments were not significantly different between the lidocaine/tetracaine patch and lidocaine/prilocaine cream.

Exploratory comparisons of the median lidocaine/tetracaine patch VAS scores for the four application times were performed using pairwise Mann–Whitney tests. There were no significant differences between 10 and 20

min or between 30 and 60 min ( $P=0.978$  and  $0.701$ , respectively). Comparisons between shorter and longer application times, looking at the differences between 10 or 20 min and 30 or 60 min, were all statistically significant at  $P<0.05$ , indicating improved analgesia with extended exposure to the lidocaine/tetracaine patch.

The lidocaine/tetracaine patch was associated with significantly more erythema than was lidocaine/prilocaine cream at 20, 30, and 60 min ( $P=0.035$ ,  $0.041$ , and  $0.004$ , respectively), whereas lidocaine/prilocaine cream produced significantly more blanching than did the lidocaine/tetracaine patch at 30 and 60 min ( $P<0.05$ ). Both treatments were well tolerated. The only AE reported was nausea and faintness that occurred in two subjects (one subject in the 10 min treatment group and one subject in the 60 min treatment group). These AEs were considered moderate in severity, unlikely related to the study treatments, and were attributed to the vascular access procedure. The subject from the 10 min treatment group refused the second vascular access procedure and was withdrawn from the study. Only one subject in the 20 min group experienced slight oedema with both treatments. No delayed skin reactions were reported.

## Discussion

The lidocaine/tetracaine patch provided significantly better dermal anaesthesia than did lidocaine/prilocaine cream after 10, 20, and 30 min application times. Consistent with this, significantly more subjects in those three groups reported that they would use the lidocaine/tetracaine patch again compared with lidocaine/prilocaine cream, and more subjects reported no pain associated with the vascular access procedure after 20 or 30 min applications of the lidocaine/tetracaine patch than after applications of the same length of lidocaine/prilocaine cream.

The design of this study attempted to ensure that the investigator and subject remained blinded to the choice of anaesthetic treatment applied to each arm by including lidocaine/prilocaine cream-naïve subjects and third-party application of the interventions. One aspect of therapy, the heat associated with the lidocaine/tetracaine patch, may have led to partial unblinding of the subjects. Similarly, erythema might have indicated to the investigator that the applied treatment was less likely to be lidocaine/prilocaine

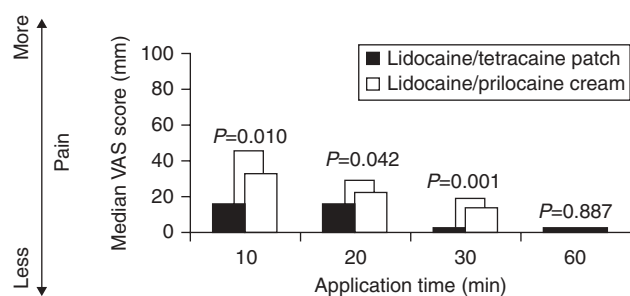


Fig 2 Subject VAS scores in the two groups.

Table 2 Subject-reported general assessments of effectiveness of the lidocaine/tetracaine patch and lidocaine/prilocaine cream before a vascular access procedure

Treatment group	Per cent indicating anaesthetic eliminated pain			Per cent indicating they would use product again		
	Lidocaine/tetracaine patch	Lidocaine/prilocaine cream	P-value	Lidocaine/tetracaine patch	Lidocaine/prilocaine cream	P-value
10 min (n=20)	65	42	0.059	80	47	0.008
20 min (n=20)	90	60	0.014	95	70	0.025
30 min (n=22)	95	64	0.020	100	64	0.005
60 min (n=20)	95	95	1.000	90	95	0.317

cream, since knowledge of previous experience could not be avoided. Despite these limitations, the subject-reported efficacy endpoints provide a clear demonstration of the anaesthetic superiority of the lidocaine/tetracaine patch with 10, 20, and 30 min applications. As would be expected, the subjects reported similar experiences after application of each treatment for 60 min, indicating that these study limitations do not compromise the conclusions that can be drawn from the results. Other limitations that could have affected the outcome of the study include control of room temperature and control of the amount of lidocaine/prilocaine cream applied under the plastic template. Although use of the plastic template that covered the same area as the lidocaine/tetracaine patch limited the amount of lidocaine/prilocaine cream applied to a certain extent, it is possible that the cream could have been more or less thinly applied each time.

The results of this study are consistent with those of other studies of the lidocaine/tetracaine patch. The lidocaine/tetracaine patch has been shown to provide effective dermal anaesthesia *vs* placebo in adults<sup>3 11 12</sup> and children.<sup>13</sup>

Given the limitations of our study, the results suggest that the combination of a eutectic mixture of anaesthetics within a heated-patch delivery system is likely to provide a more rapid onset of local anaesthesia than is possible with anaesthetic cream formulations. Comparison of the lidocaine/tetracaine patch with and without the heating element has demonstrated more effective analgesia with the heating element (Masud and colleagues, unpublished data).

Of note, the lidocaine/tetracaine patch produced significantly more erythema than did lidocaine/prilocaine cream, which may indicate a useful vasodilatory effect regarding vascular access procedures. Tetracaine produces vasodilatation rather than vasoconstriction, which may make the small veins on the dorsum of the hand more prominent and, thus, easier to access. In contrast, the vasoconstrictive properties of prilocaine may decrease the visibility of veins, making vascular access procedures more difficult with lidocaine/prilocaine cream. Previous studies have also found tetracaine to produce significantly more erythema than lidocaine/prilocaine cream,<sup>14</sup> and in a study of 36 volunteers, tetracaine was associated with easier i.v. cannulation than with lidocaine/prilocaine cream.<sup>15</sup> In our study, vascular access was achieved at the first attempt in all but four subjects with each treatment, but this is perhaps not surprising since the site of venepuncture was not at a limb extremity. Further studies are warranted to elucidate whether this vasodilatory effect translates into meaningful clinical benefit in terms of facilitating venous access in more challenging circumstances.

In this study, both the lidocaine/tetracaine patch and lidocaine/prilocaine cream were well tolerated and there was nothing to distinguish between treatments regarding AEs other than the differences in erythema and blanching. Skin reactions are not uncommon after treatment with a local topical anaesthetic, and erythema, blanching, and

oedema have been reported to be the most common skin reactions in 1449 individuals treated with the lidocaine/tetracaine patch in multiple clinical studies.<sup>4</sup> The lidocaine/tetracaine patch is a single-unit dose that delivers a known amount of drug onto a clearly defined area of skin. Case reports in the literature have described lidocaine toxicity resulting from grossly excessive doses of lidocaine/prilocaine cream applied to children by parents before arriving at a medical appointment.<sup>16</sup> The potential of the lidocaine/tetracaine patch for accidental overdose is substantially reduced by the use of a fixed amount of anaesthetic applied to a limited surface area.

The lidocaine/tetracaine patch produced substantial improvements in the level of analgesia compared with lidocaine/prilocaine cream, even when administered for only 10 min. The lidocaine/tetracaine patch appears to be well suited for topical dermal anaesthesia in a broad spectrum of clinical settings. The substantial improvement in onset of action has the potential for a wide variety of benefits in clinical practice. These include the opportunity to provide rapid, non-invasive analgesia in an emergency or time-constrained setting; lessening the constraints on provision of topical analgesia for elective procedures; and more convenient administration by eliminating the time required to apply the occlusive dressings required for anaesthetic creams. These aspects of topical anaesthesia with the lidocaine/tetracaine patch warrant further exploration in the clinic.

## Acknowledgements

The authors acknowledge the assistance of Luana Atherly, PhD, and Erika L. Meyer, PhD, in the preparation of this manuscript.

## Funding

This work was supported by a grant from ZARS Pharma, Salt Lake City, UT, USA.

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