Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia

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Summary
Post-herpetic neuralgia (PHN) is a common and often intractable neuropathic pain syndrome predominantly affecting the elderly. Topical local anesthetics have shown promise in both uncontrolled and controlled studies. Thirty-five subjects with established PHN affecting the torso or extremities completed a four-session, random order, double-blind, vehicle-controlled study of the analgesic effects of topically applied 5% lidocaine in the form of a non-woven polyethylene adhesive patch. All subjects had allodynia on examination. Up to 3 patches, covering a maximum of 420 cm², were applied to cover the area of greatest pain as fully as possible. Lidocaine containing patches were applied in two of the four 12-h-long sessions, in one session vehicle patches were applied, and one session was a no-treatment observation session. Lidocaine containing patches significantly reduced pain intensity at all time points 30 min to 12 h compared to no-treatment observation, and at all time points 4-12 h compared to vehicle patches. Lidocaine patches were superior to both no-treatment observation and vehicle patches in averaged category pain relief scores. The highest blood lidocaine level measured was 0.1 µg/ml, indicating minimal systemic absorption of lidocaine. Patch application was without systemic side effects and well tolerated when applied on alldynic skin for 12 h. This study demonstrates that topical 5% lidocaine in patch form is easy to use and relieves post-herpetic neuralgia.

Key words: Post-herpetic neuralgia; Topical therapy; Lidocaine; Controlled trial; Neuropathic pain; Local anesthetic

Introduction
Post-herpetic neuralgia (PHN) is a common and difficult to manage neuropathic pain syndrome (Hope-Simpson 1965; Rowbotham 1994). Many of the predominantly elderly patients with PHN cannot tolerate tricyclic antidepressants, the only oral medication class proven effective because of pre-existing cognitive impairment, cardiac disease, or systemic illness (Watson 1993a). Anticonvulsants, non-narcotic analgesics, and opioids may be effective in selected patients, but also have significant side effects. Once PHN is established, invasive local anesthetic blocks are unlikely to provide more than temporary relief (Dan et al. 1985).

In uncontrolled studies, simple subcutaneous infiltration of the area of pain with lidocaine can relieve pain for periods of hours to weeks (Secunda et al 1941; Rowbotham and Fields 1989a). There is pathological evidence that cutaneous branches of sensory nerves are affected in PHN (Ebert 1949; Muller and Winkelmann 1969), but the stratum corneum of intact skin presents a formidable barrier for drug delivery. The only topically effective preparations in blocking pain from experimentally induced sunburn and painful electrical stimulation contain the base form of the local anesthetic drug (Dalili and Adriani 1971). Three uncontrolled studies of topical local anesthetics for PHN have shown benefit using formulations of 10% lidocaine base in a gel vehicle, 10% lidocaine base in glycerin, and a mixture of lidocaine base and prilocaine (Rowbotham and Fields 1989b; Kissin et al. 1989; Stow et al. 1989).

Topical application directly on the area of greatest pain should provide the safest and most efficient treatment if activity generated in damaged or sensitized cutaneous sensory nerves is critically important for maintaining the pain in some patients with PHN. In a randomized, double-blind study, our group demonstrated the efficacy of 5% lidocaine
gel (Lidoderm gel™) compared with gel vehicle in PHN patients with painfully sensitive skin (Rowbotham et al. 1995). By using a control session of remote application of the same amount of lidocaine gel in addition to a vehicle application session, lidocaine gel was demonstrated to relieve pain through a direct action on painful skin.

The problem of how to best deliver the local anesthetic to the area of painful skin remains unresolved. In our previous controlled study, an occlusive dressing (Tegaderm™) was used to enhance penetration by keeping the gel in contact with the skin (and away from clothing). However, in elderly patients who have fragile, painfully sensitive skin, occlusive dressings are poorly tolerated because they trap heat and perspiration, may produce adhesive burns when removed, and are cumbersome to apply. Allodynia, usually manifested clinically as painful sensitivity to contact with clothing and touch, is a major problem for the majority of patients with PHN. With this in mind, the 5% lidocaine gel was reformulated into a patch (Lidoderm patch™), consisting of a soft, stretchy, non-woven polyethylene backing with a drug-containing adhesive layer. This new formulation was tested in a randomized, double-blind, four-session study designed to assess analgesic effects of both drug and vehicle compared to observation only.

Methods

Subjects

Subjects were eligible if they had PHN, defined as pain present more than 1 month after healing of the skin rash, and had a well-defined area of painfully sensitive (allodynic) skin on the torso or limbs. Subjects were required to be in stable health, without medical contraindications to topical local anesthetic application, and without neurolytic or neurosurgical therapy for PHN. All subjects gave informed consent prior to participation, and the study was approved by the Committee on Human Research at the University of California, San Francisco.

Study sessions

The study set up is shown in Fig. 1. Subjects were randomized as to session order, stratified by gender. The four study sessions were of three types. Two sessions consisted of lidocaine patch application on the area of greatest pain and one session consisted of vehicle patch application. One session was a no-treatment, observation only session.

Any use of topical medications for PHN, including capsaicin and steroids, was discontinued at least 2 weeks prior to the first study session. During the study, subjects were not allowed to use any topically applied medications, salves, etc., on the area affected by PHN. Subjects were allowed to continue use of oral medications for control of PHN pain, including 'as needed' analgesics, but were not allowed to start new oral medications during the study. Subjects kept a daily pain diary throughout the study in which they recorded an overall pain level for that day and all medications taken for control of PHN pain.

All sessions were carried out at the UCSF Pain Clinical Research Center. All sessions requiring patch application were carried out in an identical double-blind manner. Data collection for the observation only sessions followed the same format as patch application sessions except no blood was drawn for lidocaine level. Sessions were at least 72 h apart and were typically scheduled 1 week apart. If a subject experienced prolonged relief from one of the sessions, the next session was delayed until pain returned to at least 75% of their average pain level prior to entering the study. If skin irritation was noted at the end of a session, the subject was re-examined the following day and further test sessions were postponed until skin irritation resolved fully.

For the first 6 h of patch application or no-treatment observation sessions, subjects were dressed and ambulatory, but remained on the medical center campus in the vicinity of the Pain Clinical Research Center. After the 6 h ratings, including blood drawing and brief removal of the patches for skin inspection, the patches were reapplied and the subjects were sent home. At home, the subjects made additional ratings of pain, pain relief, and side effects at 9 h and 12 h after initial application before finally removing the patches.

Study drug and vehicle

Lidocaine patches (Lidoderm patch™, Hind Health Care, Sunnyvale, CA) contain an adhesive of 5% lidocaine base (700 mg/patch), water, glycerin, d-sorbitol, sodium polyacrylate, sodium carboxymethylcellulose, propylene glycol and other ingredients on a non-woven polyethylene backing. Vehicle patches are identical except for the absence of lidocaine. The size of a single patch is 10 x 14 cm.

Patch application

Prior to patch application, the painful area to be treated was marked and then photographed based on the subject's report of (1) the borders of the area of sensory abnormality, and (2) the area of greatest pain. Up to 3 patches (420 cm² of patch area) were applied to cover the area of greatest pain as fully as possible. Allodynia to gentle stroking of the skin with a cotton swab, a requirement for study participation, was graded as absent (0), mildly painful (+1), moderately painful (+2), or severely painful (+3).
Pain ratings

Pain intensity was assessed using a horizontal 100 mm visual analog scale (VAS). The subject indicated the severity of his or her pain with a mark along the line between 0 = no pain and 100 = worst pain imaginable. Prior to patch application, VAS scores were obtained 2–3 times over a 45 min period. After patch application, VAS scores were obtained at 30 min, 1 h, 2 h, 4 h, 6 h, 9 h, and 12 h.

Pain relief was assessed using a category scale consisting of 6 sentences indicating that: 0 = the pain is ‘worse’, 1 = ‘no’ pain relief, 2 = ‘slight’ pain relief, 3 = ‘moderate’ pain relief, 4 = ‘a lot’ of pain relief, and 5 = ‘complete’ relief of pain. As the scale is designed to assess changes, the baseline pre-application rating is assumed to be ‘no’ relief of pain (score 1). After patch application, category relief scores were obtained at 30 min, 1 h, 2 h, 4 h, 6 h, 9 h, and 12 h. Because no patches were applied during the no-treatment observation only session, the scale was modified to indicate worsening or improvement relative to the beginning of the observation session and ratings were obtained at the same time points.

Symptom Checklist (SCL) and skin inspection

Side effects were rated using a written list of 27 items (maximum score 91). Most of the symptoms were included to screen for effects associated with blood lidocaine levels at or above the antiarrhythmic range, but also overlap with common effects of tricyclic antidepressants and systemic angesics. SCL scores were obtained at the same times after patch application as the VAS and relief scores. A brief examination of the skin under the patches was carried out after 6 h to document skin redness, blanching, or irritation.

Blood lidocaine levels

Blood samples were drawn into heparinized tubes prior to patch application and at 1 h, 4 h, and 6 h after patch application. The blood was centrifuged and the plasma extracted and refrigerated at 5°C until transfer to a −20°C freezer for longer term storage before assay. Venous blood lidocaine was assayed using one of two techniques. The TDX system (Abbott Laboratories) is an antigen-antibody assay sensitive to levels as low as 10 ng/ml, but only able to reliably quantitate above 100 ng/ml. The usual minimum anti-arrhythmic concentration of lidocaine in the venous circulation is 1000–1500 ng/ml (Benowitz and Meister 1978). A more sensitive assay was performed in the Clinical Pharmacology Laboratory at San Francisco General Hospital using capillary gas chromatography with nitrogen-phosphorus detection that reliably quantitates to levels as low as 10 ng/ml (Jacob et al. 1991).

Data Analysis

Statistical analyses were performed by John S. Quiring, Ph.D., of QST Consultations (Allendale, MI). The analysis was based on an ANOVA which corresponded to the 4-way crossover design with treatments at three levels: lidocaine, vehicle, and observational. For analysis purposes the first and second lidocaine patch sessions were coded together. The statistical model included the effects of patient (nested within sequence), treatment, sequence and session. A hypothesis test was conducted to determine if there was any evidence of a carryover (sequence) or residual effect of the treatment administered in one session on the results observed in the next session. The least-squares means, obtained by application of ANOVA, were used as the best unbiased estimate of the patients’ mean values considering the patient, sequence, and session effects present in the study.

All tests of hypotheses which evaluated the equality of treatments were based on the type III mean square error terms. An overall F test was conducted to determine if there were differences among the three treatments. Additionally, pairwise contrast tests between treatments were performed to evaluate the statistical significance between pairs of treatments. The difference between two treatments (F test) was considered statistically significant if both the overall and pairwise P values were less than or equal to 0.05. For pain intensity VAS scores and SCL scores, the pairwise comparisons were made at individual time points in addition to the overall F test. For the limited number of rating choices present in the category relief scores, the scores were averaged over all time points after patch application for pairwise comparison in addition to the overall F test.

Results

Subjects

Forty subjects were recruited and 35 subjects completed the study. Only one of the drop-outs was exposed to either the lidocaine patch or vehicle patch; this subject was dropped by the investigators after completing one lidocaine patch session and the observation session because severe depression interfered with obtaining reliable ratings. One subject withdrew consent before the study sessions began, one failed to meet eligibility criteria at the first session, and 2 subjects whose first session was observation only dropped out after that session.

A total of 20 men and 15 women completed the study. The age range was 50–90 years and the mean age was 75. The duration of PHN ranged from 4 to 318 months, with a mean duration of 48 months. The mean size of the area of greatest pain was 255 cm², with a range from 80 to 750 cm². In only 3 subjects was the area of greatest pain larger than the 420 cm² maximum area that could be covered by 3 patches. As a group, the subjects had moderate allodynia (mean: 1.6 on a 0–3 scale). In individual subjects, the mean allodynia rating for the four sessions ranged from 0.25 to 2.50.

Pain ratings

Pre-treatment, the least-square mean pain intensity VAS scores were 49.3 mm for lidocaine patch sessions, 48.4 mm for vehicle patch sessions, and 47.2 mm for observation only sessions (P = NS). Changes from average pre-treatment VAS at all time points and the average change in the least-square means VAS scores are shown in Fig. 2. During the lidocaine sessions, the greatest reduction in VAS pain intensity was 12.3 mm at the 4 h time point, with the average reduction in VAS across all time points being 10.2 mm. Compared to observation only, lidocaine patch application significantly reduced pain at all time points 30 min to 12 h (individual time points P = 0.0001 to P = 0.021). Compared to vehicle patch, lidocaine patch application significantly reduced pain at time points 4 h, 6 h, 9 h, and 12 h (individual time points P < 0.001 to P = 0.038). Vehicle patch significantly reduced pain compared to observation only at times 2 h and 6 h (individual time points P = 0.016 and P = 0.041).

The least-square means for the category pain relief scores for all sessions at all time points are shown in Fig. 3. Category pain relief scores were highest for lidocaine patch application at all time points 30 min through 12 h. The least-square mean of the average pain relief rating was
Post-application VAS scores ranged from 47 to 49 mm for ratings at home. Lidocaine patch superior to observation only at 2 h and 6 h (individual time points \( P = 0.001 \) and \( P = 0.041 \)).

The spread of category pain relief responses for the 4 and 6 h time points during the lidocaine patch sessions were as follows: worse pain—no relief (\( n = 1 \)), no relief—slight relief (\( n = 10 \)), slight relief—moderate relief (\( n = 14 \)), moderate relief—a lot of relief (\( n = 7 \)), a lot of relief—complete relief (\( n = 3 \)). Severity of allodynia at the start of the study sessions was not correlated with response to patch application.

Although a small number of subjects reported pain reduction lasting several days after a single application session, analysis of daily pain diaries for pain ratings and medication use between test sessions did not reveal a significant analgesic carryover after lidocaine patch sessions for the group as a whole.

**Symptom Checklist (SCL) and skin inspection**

SCL scores were very low at the beginning of the sessions and not significantly different between the session types, ranging from a least-squares mean of 2.49–3.06 out of a maximum of 81. There were no significant changes over time within any session type or in pairwise comparisons between session types, indicating that new symptoms suggestive of systemic local anesthetic effects did not occur.

One subject, an elderly man chronically receiving systemic steroids for asthma, had bruising and pain with patch removal. Two subjects had mild, transient (minutes to a few hours) skin reddening; one with vehicle patches and one with lidocaine patches. Subjects tolerated peeling the patches off with only minor and transient increases in pain.

**Blood lidocaine levels**

Because of venous access problems in 3 subjects, blood samples were drawn for lidocaine level in a total of 64 of the 70 sessions in which lidocaine patches were applied. In 18 sessions, lidocaine levels were analyzed with the TDX system. The highest blood level measured with the TDX assay was 70 ng/ml, below the reliable quantitation limit of the assay.

The remaining 46 sessions were analyzed using the more sensitive GC assay. Using GC, after 1 h of patch application the highest level was 12 ng/ml. After 4 h, the highest level was 53 ng/ml, and exceeded 40 ng/ml in only 7 sessions. After 6 h application, the highest level was 104 ng/ml, and exceeded 40 ng/ml in 13 sessions. For comparison, the minimum venous antiarrhythmic level of lidocaine is 1000 ng/ml.

**Discussion**

This study demonstrates that topical 5% lidocaine in patch form reduces the pain of PHN. Lidocaine containing patches were superior to vehicle patches in reducing pain intensity VAS scores and produced higher category pain relief scores. Systemic lidocaine absorption was minimal after 6 h despite the large surface area (up to 420 cm\(^2\)) covered. The highest lidocaine level recorded was still an order of magnitude below the minimum antiarrhythmic level. The patches were tolerated for a period of 12 h without systemic side effects or significant skin irritation.

The acute outbreak of zoster may damage the peripheral nerve apparatus from the dorsal root to cutaneous nerve endings (Watson and Deck 1993). Surviving, but damaged, cutaneous nociceptor fibers in the area of pain may have abnormal spontaneous activity and be sensitized to me-
mechanical or other stimuli (Cline et al. 1989; Tanelian and MacIver 1991). These changes may in part be due to accumulation of sodium channels at sites of injury, the target of local anesthetics (Devor et al. 1993). This study supports the hypothesis that low doses of lidocaine delivered through intact stratum corneum to abnormally functioning afferents relieves pain by reducing abnormal spontaneous and evoked activity. In our previous double-blind, vehicle controlled study of topical lidocaine gel for PHN (Rowbotham et al. 1995), a reduction in pain was demonstrated with lidocaine gel application under occlusion on the area of pain. Application of the same amount of lidocaine gel to the opposite side of the body in a carefully blinded manner was ineffective, proving that systemic lidocaine absorption was not responsible for the analgesic effect. Lidocaine blood levels were slightly higher with gel application than in this study of lidocaine patch application. The present study of lidocaine patches confirms and extends the findings of the lidocaine gel study by assessing the effect of both the topical anesthetic and the vehicle compared to observation only.

The majority of subjects reported pain relief, but only partial relief. Averaging the 4 and 6 h time points during the lidocaine patch sessions, 24/35 subjects reported slight or better relief, with 10 of these 24 reporting moderate or better relief. All subjects had allodynia, but the severity of allodynia prior to patch application did not predict pain relief. Consistent with the widespread peripheral nervous system injury produced by acute zoster, the partial nature of the relief reported and the lack of any response in some subjects suggests that cutaneous pain generators may not be present in some subjects and only a minor component in others.

The composition of the patch itself, being soft, stretchy and gently adherent to painfully sensitive skin, also appears to provide an element of pain reduction. The skin is protected from mechanical stimulation, including the rubbing of clothing and inadvertent touching for the duration of application of the patch, in this case 12 h. Subjectively, this was found to be soothing for the majority of subjects and confirmed by pain intensity VAS scores and category pain relief scores showing vehicle patches superior to observation only.

Compared to other methods for control of PHN pain, topical lidocaine patches have many advantages. They are easy to apply and remove, and comfortable to wear under clothing for the long duration of each study session with a low incidence of skin irritation. Patients with a large skin area affected by PHN can be treated and the patches can be cut to fit the desired area exactly. Systemic side effects were not evident; a major drawback of opioids, anticonvulsants, and antidepressants. Allodynia is a major component of the pain of PHN (Nurmikko 1994), and for some patients is so severe with the wearing of any clothing as to keep them housebound. By padding and protecting the painful area from contact, the lidocaine patches tested here would be expected to promptly and effectively allow wearing of clothing. The findings of the present study support topical local anesthetic patch application as a potentially significant therapeutic modality for PHN.

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References


