Topical Lidocaine Gel Relieves Postherpetic Neuralgia

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Postherpetic neuralgia (PHN) following herpes zoster is a common and disabling neuropathic pain syndrome. In a double-blind, three-session study, 5% lidocaine gel or vehicle was applied simultaneously to both the area of pain and to the contralateral mirror-image unaffected skin. In the local session, lidocaine gel was applied to the painful skin area. In the remote session, lidocaine gel was applied to mirror-image skin. In the placebo session, vehicle was applied bilaterally. For cranial PHN, gel was applied without occlusion for 8 hours. For limb or torso PHN, gel was applied under occlusion for 24 hours. The 16 subjects with cranial PHN reported pain relief significantly favoring local drug application at 30 minutes, 2, 4, and 8 hours. The 23 subjects with torso or limb PHN reported significantly lower pain intensity with local drug application at 8 hours and both pain relief and reduced pain intensity at 24 hours. Remote lidocaine application to mirror-image skin was no different from placebo. No systemic adverse effects were reported and blood levels did not exceed 0.6 μg/ml. Topical application of 5% lidocaine gel relieves PHN pain by a direct drug action on painful skin.

Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol 1995;37:246–253

Herpes zoster (shingles) occurs during the lifetime of 10 to 20% of all people [1, 2]. The disease is believed to result from activation of latent viral nucleic acid in dorsal root ganglion neurons. The viral particles are transported along sensory nerves to the skin to produce the characteristic dermatomal vesicular rash [2]. Cutaneous branches of the affected peripheral nerve segments become inflamed, demyelinated, and may be irreversibly damaged [3, 4]. The most common and debilitating complication of herpes zoster is postherpetic neuralgia (PHN), defined as pain persisting for more than 1 month after healing of the initial skin eruption [5–7]. More than 50% of those over the age of 60, and 70% of those over 70, will suffer from PHN after an episode of shingles [7]. Although most patients with PHN improve spontaneously within the first year, a large number continue to experience the relentlessly disabling pain for years or even a lifetime.

The only systemic medications proven effective for PHN are tricyclic antidepressants [8–13]. Although 40 to 60% of patients who complete a trial of tricyclic antidepressants achieve satisfactory relief, side effects such as orthostatic hypotension, forgetfulness, constipation, dry mouth, and sedation prove intolerable to many. Other systemic medications, including anticonvulsants, nonnarcotic analgesics, and opioids, have significant side effects and have not been proven effective for PHN [8–10, 14].

The use of local anesthetics to control the pain of herpes zoster and PHN has a history dating back to Wood's 1929 report of complete relief of ophthalmic PHN from injection of procaine into the supraorbital nerve [15]. Since that time, local anesthetics have been given to patients by the epidural route, skin infiltration, intravenously, as stellate ganglion blocks, as peripheral nerve and intercostal nerve blocks, and by other routes to control the pain of acute zoster and PHN [16–20]. However, once PHN is established, invasive local anesthetic blocks usually provide no more than temporary relief. We reported that 9 of 12 patients achieved at least 50% relief with simple infiltration of lidocaine into painfully sensitive skin [21]. These results suggested that activity generated in cutaneous nerves is essential for maintaining the pain in some patients with PHN. If the pain of PHN requires activity in the cutaneous terminals of sensory neurons, local application of an effective nerve blocking agent directly on the area of greatest pain should provide an effective and safe treatment.

The barrier presented by the stratum corneum of intact skin requires special formulations for topical drug delivery. For example, Dalili and Adriani [22]

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Received Apr 5, 1994, and in revised form Aug 26. Accepted for publication Sep 1, 1994.

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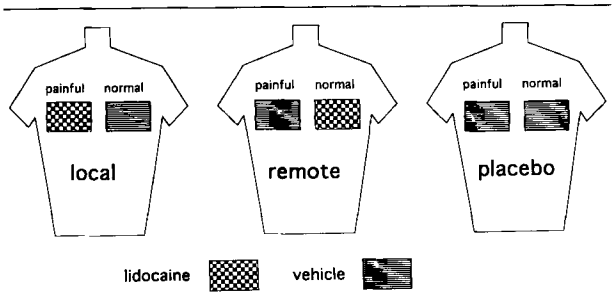

Fig 1. Experimental setup. Subjects had gel applied to both painful skin and contralateral nonpainful skin during each session. In the local session, active lidocaine gel was applied on painful skin and vehicle on normal skin. In the remote session, vehicle was applied on painful skin and active lidocaine gel on normal skin. In the placebo session, vehicle was applied bilaterally. Cranial postherpetic neuralgia (PHN) subjects had gel applied without an occlusive dressing for 8 hours. Subjects with PHN of the limbs or torso had gel applied under Tegaderm occlusion for 24 hours.

found in 1971 that for experimental cutaneous pain, the only effective topical local anesthetic preparations contained the lipophilic base form of the drug in relatively high concentration. Niamtu and co-workers [23] reported that 30% lidocaine base in cream form produced sufficient anesthesia to allow minor skin operations. Furthermore, formulations of local anesthetics designed specifically to penetrate intact skin have been shown to produce effective cutaneous analgesia [24–27]. To date, only limited and uncontrolled clinical studies of topical local anesthetics for PHN have been carried out [28–30]. Despite widely varying formulations of the vehicle, these anecdotal studies all indicated that topically applied lidocaine base is effective.

In the three-session, randomized, double-blind study reported here, 5% lidocaine gel was compared with vehicle placebo in PHN patients with painfully sensitive skin. The study design (Fig 1) was structured so that drug absorption, local toxicity, and gross sensory changes from application to undamaged skin and postherpetic skin could be compared directly. As we have previously demonstrated that intravenous lidocaine administration relieves PHN pain, we addressed the possibility that the pain relief resulting from topical application of lidocaine is due to systemic absorption [31]. To do this, we applied the gel to unaffected skin contralateral to the area affected by PHN.

Methods

Patients

Subjects were eligible if they had pain present more than 1 month after healing of the zoster skin rash, had a well-defined area of painfully sensitive skin, were in stable health, had no medical contraindications to topical local anesthetic application, and had not undergone neurolytic or neurosurgical therapy for PHN.

Any use of topical medications for PHN, including capsaicin and steroids, was discontinued at least 1 week prior to the first study session. During the study, subjects were not allowed to use any topical medications 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.

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 (UCSF).

Study Sessions

All sessions were carried out at the UCSF Pain Clinical Research Center. Subjects with PHN affecting the head or neck had gel applied without occlusion (cranial group) and sessions lasted 8 hours. Subjects with PHN of the limbs or torso had gel applied under Tegaderm occlusion (torso–limb group) and sessions lasted 24 hours. The study design is illustrated in Figure 1. One session type (local) consisted of 5% lidocaine gel (Lidoderm gel) applied to the painful skin area and vehicle placebo application to the matching contralateral skin area. One session type (remote) consisted of vehicle placebo application to the painful skin area and 5% lidocaine gel application to the matching contralateral skin area. One session type (placebo) consisted of vehicle placebo application to both the painful skin area and the matching contralateral skin area. Subjects were randomly assigned to one of the six possible treatment orders (local–remote–placebo, placebo–local–remote, etc).

All sessions were carried out in an identical double-blind manner. Sessions were at least 72 hours apart and were usually scheduled 1 week apart. If subjects 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 reexamined the following day and further test sessions were postponed until skin irritation resolved fully. Subjects were dropped from the study if all three sessions could not be completed within a 42-day time period.

Subjects remained in the vicinity of the UCSF Pain Clinical Research Center for the first 8 hours after gel application. After 8-hour ratings and skin examination, the subjects in the cranial group had gel removed and went home. After 8-hour ratings and skin examination for the torso–limb group, subjects went home and returned the following morning for final (24 hour) ratings followed by gel removal and skin examination, including sensory examination.

Drug Application

Lidocaine 5% gel (Lidoderm gel, Hind Health Care, Sunnyvale, CA) contains lidocaine, propylene glycol, neutralized carbomer, and polysorbate 20. Vehicle placebo gel was identical except for the absence of lidocaine.

To prevent the investigators from discovering the active gel, they wore gloves for application and removal. The painful area to be treated was marked (and then photographed) based on the subject's report of the borders of the maximally painful area corroborated by lightly stroking the skin with a

cotton swab. In every case, treated skin included the areas of postherpetic scarring and areas of allodynia in unscarred skin. Tegaderm is a clear, thin, elastic, and self-adherent occlusive dressing. Sheets measuring 20 × 30 cm were used. The sheets were cut so that after gel was applied to the painful area, the Tegaderm dressing would seal the area with an approximate 2-cm border around the gel application area. The procedure was then repeated on the contralateral normal skin. Up to 800 cm^2 of skin was covered with gel on each side of the torso or limbs. For the head or neck, an area of up to 200 cm^2 on each side was covered with gel.

Measures

Pain intensity ratings using a 100-mm visual analog scale (VAS) were completed twice prior to gel application. For the cranial group, VAS ratings were made at 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, and 8 hours after application. For the torso–limb group, VAS ratings were made at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours after application. A six-item category scale of pain relief (worse, no relief, slight, moderate, a lot, and complete relief) was completed at the same times after application as the VAS scale. A 27-item checklist of side effects (maximum score, 81), primarily designed to detect symptoms of systemic local anesthetic administration or other systemic medication effects, was completed at the same times as the pain VAS.

The severity of allodynia was assessed prior to gel application and after gel removal. Allodynia, defined as a painful sensation elicited by gentle moving mechanical stimulation that is innocuous in normal skin areas, was rated as absent (0), mild (+1), moderate (+2), or severe (+3). Examination of the skin for signs of skin irritation was carried out prior to gel application, at the 8-hour ratings (the occlusive dressing is clear), and after gel removal. Blood pressure and pulse were measured twice prior to gel application and repeated at 1, 4, and 8 hours after gel application in the cranial group. Blood pressure and pulse were measured twice prior to gel application and repeated at 1, 4, 8, and 24 hours after gel application in the torso–limb group.

Blood Lidocaine Levels

Blood lidocaine levels were measured prior to gel application and at 1, 4, and 8 hours after gel application in the cranial group. An additional measurement was obtained at 24 hours in the torso–limb group. For the majority of sessions, lidocaine was assayed using an antigen–antibody assay sensitive to levels as low as 0.1 μg/ml (TDX system, Abbott Laboratories Inc). For 15% of the subject sessions, lidocaine levels were measured in the laboratory of Dr Peyton Jacob III at San Francisco General Hospital using a capillary gas chromatography assay that is linear from lidocaine concentrations of 0.01 μg/ml to 1.0 μg/ml. This assay uses carbocaine as an internal standard with an extraction method adapted from the method of Jacob and coworkers [32].

Data Analysis

Statistical consultation was obtained from John S. Quiring, PhD, of QST Consultation, Ltd, Allendale, MI. Because of the slightly differing protocols for occlusion and nonocclusion subjects, results for the two groups were analyzed separately. The primary variables of interest were the pain VAS scores and the category of pain relief scores. The six categories of pain relief ratings were treated as linear equidistant points. The primary comparison was between the session with lidocaine gel on the painful area and the session with placebo vehicle on both sides. Symptom checklist (SCL) scores, blood pressure, and pulse rates were handled in the same way as the pain VAS and pain relief scores.

The method of analysis of variance (ANOVA) was used to analyze all study variables at each sampling time. This was accomplished using the Statistical Analysis System (SAS) version 6.04, under the procedure General Linear Models. The analysis of the study variables for all three sessions was based on an ANOVA that corresponded to the three-way crossover design. The statistical model included the effects of subject (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 p value for testing the equality of the local and placebo treatments was derived from the F test using the pooled ANOVA type III mean square error in the hypothesis test statement. The least-square means, which were obtained by application of ANOVA, were considered the best unbiased estimate of the subject's mean values considering the subject, sequence, and sessions effects present in the trial. The difference between placebo and local sessions were considered to be statistically significant when the p-value was less than 0.05. The change from pretreatment was computed as the pretreatment score minus the posttreatment score. If a subject had more than one pretreatment score, they were averaged.

Changes in allodynia were analyzed by subtracting the postapplication rating from the preapplication rating to give a change score (possible range, +3 to −3). Statistical significance of the change in allodynia for each type of test session was determined by the Wilcoxon signed ranks test.

Results

Subjects

Fifty subjects were recruited for participation in the study. Thirty-nine subjects completed all three sessions without protocol violation or ineligibility and are included in the data analysis as evaluable subjects. Three subjects were recruited but did not give written consent and so did not begin any study sessions. One subject was found ineligible due to incorrect diagnosis. Two subjects repeatedly used medicated topical agents and were dropped from the study. Two subjects experienced skin redness and tenderness after the first session and declined to return for further sessions; both had received placebo vehicle application and had adhesive abrasions from Tegaderm removal. One subject reported a general flare in pain in the days following the first session without localized skin reaction and declined to return for further sessions; she had received lidocaine gel on the painful area. Two subjects could not complete the study within the 6-week limit, 1 because of scheduling problems and the other because of prolonged relief from the second session.

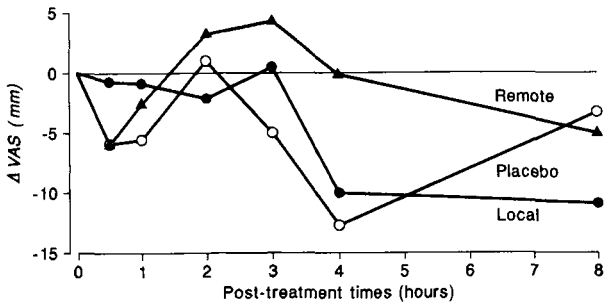

Fig 2. Cranial group, change in pain intensity visual analog scale scores. Least-square mean change computed as posttreatment score minus pretreatment score. A negative change indicates reduced pain intensity. No significant differences between local and placebo application.

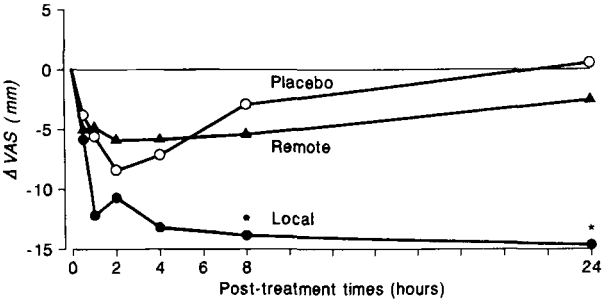

*Fig 3. Torso–limb group, change in pain intensity visual analog scale scores. Significant differences between local and placebo application are shown at 8 hours and 24 hours (*p < 0.05).*

Seven men and 9 women in the cranial group completed the study. Their average age was 75 years (range, 62–85 yr), and their average duration of PHN was 36 months (range, 6–137 months). Two subjects had PHN in the C2-3 dermatomes, the remainder in the first trigeminal division. The average area of affected skin treatment with gel was 103 cm^2. From 2.5 to 12.0 gm of gel (125–600 mg of lidocaine base) was used to fully cover the area of pain.

Eleven men and 12 women in the torso–limb group completed the study. Their average age was 70 years (range, 55–83 yr), and their average duration of PHN was 23 months (range, 4–75 months). Three patients had PHN primarily affecting the upper arm, 1 subject had PHN primarily affecting the posterior thigh, and the remaining 19 had PHN affecting the thoracoabdominal region. The average area of affected skin treated with gel was 297 cm^2, with the maximum area of skin covered by gel being 800 cm^2. From 6.5 to 12.5 gm of gel (325–625 mg of lidocaine base) was used to fully cover the area of pain.

Pain Intensity Visual Analog Scale Ratings

In the cranial group, preapplication VAS scores were 38.8 mm for the local session, 45.0 mm for the placebo session, and 42.7 mm for the remote session; these differences were not significant. Figure 2 shows the changes in the least-square mean VAS scores after gel application. Pain intensity VAS scores changed little during the first 3 hours. At the 4-hour rating, VAS scores fell by more than 10 mm in both the local and placebo sessions, but only in the local session was the reduced VAS score maintained to the 8-hour rating. Comparing the local and placebo sessions, and comparing the remote and placebo sessions, none of the postapplication VAS scores differed significantly.

In the torso–limb group, preapplication VAS scores were 51.4 mm for the local session, 49.3 mm for the placebo session, and 48.4 mm for the remote session; these differences were not significant. Figure 3 shows the changes in least-square means for VAS scores during the 24 hours of observation after gel application. Pain intensity ratings declined steadily during the first 2 hours after gel application during all three session types, but declined most during the local session. Pain ratings then gradually returned toward the preapplication baseline during both the placebo and remote sessions. During the local session, pain VAS scores continued to decline during the rest of the 24 hours of observation to levels of 13.2, 13.8 and 14.6 mm below baseline at the 4-hour, 8-hour, and 24-hour ratings. Comparing the local and placebo sessions, there was a statistically significant reduction in pain VAS ratings at 8 hours ($p = 0.048$) and 24 hours ($p = 0.024$) during the local session. There were no significant differences between the remote and placebo sessions.

Pain Relief Category Scores

In the cranial group, mean relief ratings varied between "no relief" and "slight relief" in both the placebo and remote sessions during the 8 hours of observation. Mean relief ratings during the local session were consistently higher than in the placebo and remote sessions, varying between slight relief and "moderate relief" at the 2-hour, 3-hour, 4-hour, and 8-hour ratings (Fig 4). Comparing the local and placebo sessions, there was statistically significant pain relief during the local session at 30 minutes ($p = 0.046$), 2 hours ($p = 0.010$), 4 hours ($p = 0.033$), and 8 hours ($p = 0.003$). There were no significant differences between the remote and placebo sessions.

In the torso–limb group, mean relief ratings clustered around slight relief during the first 4 hours after application during all three session types. Thereafter, relief ratings were greatest during the local session, reaching the midway point between slight relief and moderate relief at 24 hours. Comparing the local and placebo sessions, pain relief during the local session approached statistical significance at 8 hours ($p = 0.053$) and was significant at 24 hours ($p = 0.012$) (Fig

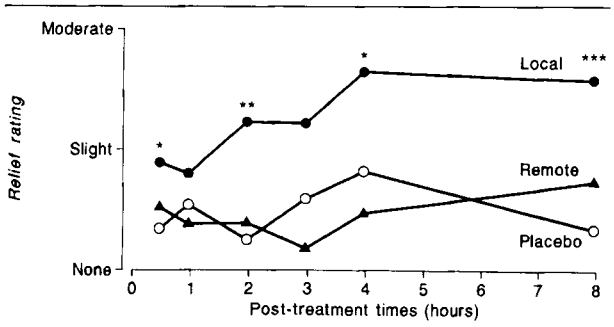

*Fig 4. Cranial group, category relief ratings. Least-square mean ratings shown for all three session types. Local treatment is superior to placebo treatment at 30 minutes, 2, 4, and 8 hours (*p < 0.05, **p < 0.01, ***p < 0.005).*

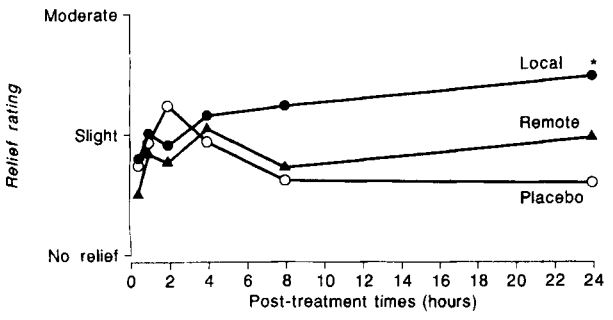

*Fig 5. Limb–torso group, category relief ratings. Least-square mean ratings shown for all three session types. Local treatment is superior to placebo treatment at 24 hours (*p < 0.05).*

5). There were no significant differences between the remote and placebo sessions.

Changes in Allodynia Following Gel Application

No subject had normal sensation in the area of pain prior to gel application, as at least mild allodynia was a requirement of study participation. In addition to the presence of allodynia, all subjects had subjective asymmetries in one or more modalities of detection threshold to light touch with a cotton wisp, perception of gentle pinprick, and perception of a chilled metal disk applied within the area of maximum pain. Mean allodynia ratings prior to gel application ranged between 2.1 and 2.2 for all three session types, indicating moderate to severe allodynia. Allodynia declined by a mean of 0.47 grades after local gel application, by 0.14 grades after placebo application, and by 0.31 grades with remote lidocaine gel application. Local gel application reduced allodynia significantly more than placebo gel application (Wilcoxon signed ranks test, $p = 0.021$). Comparing the remote and placebo sessions, changes in allodynia were not significantly different.

Skin Reactions

Mild and transient reddening of the skin was the most common skin reaction observed after gel application. No difference was observed in frequency between active gel and placebo vehicle; subjects who displayed mild skin reddening frequently developed it with both active and placebo application, indicating a reaction to a component in the vehicle. Of the total 47 subjects who had gel applied on at least one session, 29 subjects had no skin reddening during or after any session. Reddening lasting more than 24 hours was reported or observed in 3 subjects, with none developing skin breakdown. In the torso–limb group where an occlusive covering of Tegaderm was used, abrasions from the removal of the covering was a more significant problem; adhesive abrasions were reported by 9 subjects and in 2 were sufficient to cause them to drop out of the study.

Symptom Checklist Scores

Prior to drug application, most items checked on the 27-item SCL reflected either tricyclic antidepressant side effects or primary symptoms of PHN, such as "itching" and "burning skin." Preapplication SCL scores were low in both the cranial and torso–limb groups for all session types (range of least-square means, 2.9–4.6 of a possible maximum of 81). After drug application, mean SCL score changes were small (range, −0.3 to +2.6), indicating an absence of systemic local anesthetic type side effects from lidocaine gel application on either the area of pain or the contralateral matching skin area. The number of subjects who reported itching and burning skin declined during the local session in both the cranial and torso–limb groups. In the torso–limb group at 24 hours after application, the SCL was significantly lower during the local session than during the placebo session.

Blood Pressure and Pulse Measurements

There were minor changes in systolic and diastolic blood pressure, and in pulse rate, during the study sessions. Least-square mean changes in systolic blood pressure varied between −11 and +2 mm Hg. Least-square mean changes in diastolic blood pressure varied between −5 and +5 mm Hg. Least-square mean changes in pulse varied between −5 and +10 beats per minute. The changes observed did not appear to be related to session type or drug application. In the torso–limb group, both systolic and diastolic blood pressure declined to a greater degree during the local session than in the placebo session, reaching statistical significance for diastolic blood pressure at 24 hours.

Lidocaine Blood Levels

Blood lidocaine levels were all below 0.6 μg/ml. Of the 42 subjects who had any blood lidocaine levels

during local or remote sessions determined with the TDX assay, only 8 had any blood concentrations exceeding 0.1 μg/ml, with the highest measured level being 0.29 μg/ml. The TDX antigen–antibody assay cannot quantitate reliably enough below 0.1 μg/ml to calculate pharmacokinetic parameters.

Of the 13 subjects who had any blood lidocaine levels determined by the more sensitive capillary gas chromatography (quantitation limit, 0.01 μg/ml), only 3 had any levels exceeding 0.1 μg/ml with the highest recorded level being 0.59 μg/ml. By gas chromatography, measurable blood lidocaine was present at 1 hour after lidocaine gel application in only 2 of the 13 subjects. Seven of the 13 subjects did not have measurable blood lidocaine until the 8-hour blood sample. As only 3 subjects in the cranial group had lidocaine levels determined by the gas chromatography method, no absorption comparison can be made between lidocaine gel application on the highly vascular facial skin without occlusion and the thicker, less vascular skin on the torso with an occlusive dressing. There were 5 subjects who had both the local and remote sessions analyzed by the gas chromatography technique. Blood lidocaine levels during the two sessions in these 5 subjects were highly correlated ($R^2 = 0.940$, $p = 0.006$), indicating that if systematic differences in lidocaine absorption across intact versus postherpetic skin exist, they must be small.

Discussion

Lidocaine gel 5% produced significant reductions in pain intensity and significant pain relief when applied under occlusion to the torso or limbs for a period of 24 hours. When applied to the face, head, or neck region without occlusion for a period of 8 hours, significant pain relief was reported. Although complete anesthesia of the skin was not apparent after prolonged application, there was a significant reduction in allodynia with local gel application on the painful skin. No systemic side effects were reported. Local side effects consisted of mild and transient skin reddening, most likely due to the anhydrous nature of the vehicle and its components, and adhesive abrasions from the occlusive dressing used. Although there is measurable uptake of lidocaine into the venous circulation in some patients, the levels are low. Even after 24 hours of contact under occlusion, venous lidocaine levels never entered the reported range of 0.6 to 2.0 μg/ml minimum concentrations of lidocaine for antiarrhythmic effects [33]. Systemic absorption was nearly identical in normal and postherpetic skin. However, persons with nonintact skin (as in acute herpes zoster) or hepatic failure could develop significantly higher blood lidocaine levels.

Skin thickness and vascularity affect the onset and duration of analgesia observed in the present study. Arendt-Nielsen and colleagues [34] have elegantly demonstrated such relationships for EMLA (eutectic mixture of local anesthetics) [24] under occlusion using argon laser heat stimulation of the skin [34]. Areas with thick stratum corneum, such as the hand and antecubital fossa, had a slower onset of analgesia than the back, which has a thinner epidermis but similar blood flow. Areas of high vascularity, such as the forehead, had a rapid onset of analgesia but a short duration. This finding can be explained by the location of the main portion of the cutaneous free nerve endings (which include nociceptors) at the dermal–epidermal junction close to the papillary capillaries. If the vascular uptake of local anesthetic is high, the concentration around the nerve endings will remain low and produce inadequate analgesia. Vascularity is also an important determinant of the duration of analgesic effect. In areas of relatively low blood flow, analgesia may continue for a time after the drug is removed from the skin surface because the skin acts as a drug reservoir. In areas of high vascularity, the rate of vascular uptake may be equal to influx of drug through the skin and no reservoir is formed. In the present study, consistent with the more rapid drug penetration through the skin of the forehead, subjects with cranial PHN reported significant pain relief from lidocaine gel application on painful skin at 30 minutes after application. When applied to the torso or limbs, pain relief was significant and long lasting, but of apparently slower onset. The greatest difference from placebo in pain intensity and relief ratings occurred at 24 hours.

Pain intensity ratings declined during the first 2 hours in all three session types when either active or vehicle gel was applied under occlusion. This is likely due in part to prevention of the type of gentle mechanical deformation of hair follicles and skin that produces allodynia on examination and is reported by patients as painful sensitivity to touch and wearing clothing. The similarities of the session types in the first few hours after application on scales of pain intensity, pain relief, and side effects also indicates that subjects were adequately blinded as to identity of the gel. Later during the sessions, pain ratings returned toward baseline when placebo vehicle had been applied on painful skin, but pain continued to lessen in those sessions where active lidocaine gel had been applied on the painful skin. This divergence between lidocaine gel and vehicle took place at about the time that measurable blood lidocaine levels appeared. Thus, lidocaine penetration and intradermal reservoir formation probably takes place over several hours in the low vascularity, thicker stratum corneum skin areas where gel was applied under occlusion. Once established, it then persists for the remainder of the 24 hours of application and is correlated with the prolonged pain relief observed.

Comparing the remote session, in which lidocaine

gel was applied to the contralateral normal skin, with the placebo session showed no significant differences in pain intensity or pain relief. This demonstrates that a local action of lidocaine on the painful skin is necessary for its pain-relieving action. Primary afferents, including nociceptors, in damaged peripheral nerves have lowered thresholds and develop spontaneous activity [35–37]. These changes may be due in part to the increased expression of voltage-sensitive sodium channels, which are the target of local anesthetics [38]. In fact, the spontaneous activity that develops in damaged primary afferents is blocked by local anesthetics at concentrations lower than required to block impulse propagation in undamaged axons [36, 39, 40]. It is possible that with topical application of lidocaine, the tissue concentrations of the drug in the region of cutaneous nerve endings would be high enough to block abnormal spontaneous discharge without the production of a dense cutaneous anesthesia.

The mechanism of pain generation in PHN is unknown. The present results provide evidence that spontaneous activity generated in the cutaneous terminals of primary afferents makes an essential contribution to the pain of some patients with PHN. Thermography has revealed skin warming in the area of allodynia and maximal pain, possibly resulting from release of vasodilating peptides that are present in small diameter primary afferents [21, 41].

Although our evidence strongly supports the hypothesis that topical lidocaine acts locally, it is also possible that the small amount of lidocaine that is systemically absorbed contributes significantly to the observed relief reported by our subjects. Systemically administered local anesthetics have demonstrated efficacy for a variety of pain problems, including PHN [31, 42, 43]. Furthermore, animal studies indicate that such drugs can act either in the central nervous system or on damaged primary afferents in the periphery [36, 38, 39, 44]. It may be that in patients with pain due to damaged peripheral nerves, topical local anesthetics relieve pain through a combination of central and peripheral nervous system actions [45].

The 50 subjects initially recruited for this study have been followed for up to 30 months. Forty-two of the 50 elected to try topical lidocaine in open-label use. Six subjects reported minor redness and skin irritation. Thirty-one subjects used topical lidocaine for more than 2 months, and 23 of these 31 subjects reported moderate or better pain relief by follow-up examination and/or questionnaire. Although these follow-up data support a role for topical lidocaine as long-term therapy for PHN, controlled, prospective studies are needed.

In summary, topically applied lidocaine base in a gel vehicle proved effective in the single session setting for treatment of PHN pain. Side effects are minor, and blood levels of lidocaine are below the minimum antiarrhythmic concentration [25, 28, 30]. In this study, the first double-blind, vehicle-controlled study of topical local anesthetics in neuropathic pain, lidocaine gel 5% (Lidoderm gel) relieved the pain of PHN apparently through a local effect on spontaneously active primary afferents in painful skin.

Supported by a gift from Harry Hind and NIH Pain Research Training Program grant NS07265.

We thank Kurt V. Miller, MD, Bradley S. Galer, MD, Christina Verkempinck, RN, Lori Reisner-Keller, Pharm D, Susan Jardin, Lael Carlson, Dylan Mills, and 3M Corporation for their valuable contributions.

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