Effectiveness, Tolerability, and Impact on Quality of Life of the 5% Lidocaine Patch in Diabetic Polyneuropathy

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Background: The treatment of painful diabetic polyneuropathy (DPN) is often inadequate and frequently limited by the systemic adverse effects of medications, necessitating the evaluation of novel treatments.

Objective: To evaluate the effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in painful diabetic polyneuropathy.

Design: Open-label, flexible-dosing, 3-week study with a 5-week extension.

Setting: Outpatient clinics and clinical research centers.

Patients: Volunteer sample of 56 patients with clinically defined painful diabetic polyneuropathy of longer than 3 months' duration.

Intervention: The 5% lidocaine patch, with a maximum of 4 patches daily for 18 hours.

Main Outcome Measures: Change in mean daily pain diary ratings from baseline to week 3. Secondary end points included assessments of safety, tolerability, and quality of life.

Results: Patients with painful diabetic polyneuropathy showed significant improvements in pain and quality-of-life outcome measures during a 3-week treatment period. These benefits were maintained in a subgroup of patients treated for an additional 5 weeks, during which taper of concomitant analgesic therapy was permitted. Adverse events were minimal, and systemic accumulation of lidocaine did not occur.

Conclusions: Up to four 5% lidocaine patches for up to 18 h/d are well tolerated in patients with painful diabetic polyneuropathy, significantly improve pain and quality-of-life ratings, and may allow tapering of concomitant analgesic therapy. Given the open-label design of this trial, a randomized controlled trial is necessary to confirm these results.

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Neuropathic pain is a common, often disabling feature of diabetic polyneuropathy (DPN). The treatment of painful DPN is often inadequate and limited by the systemic adverse effects of currently available regimens. The 5% lidocaine patch has approval of the US Food and Drug Administration for the treatment of postherpetic neuralgia. Potential advantages of the 5% lidocaine patch in DPN are its lack of systemic adverse effects and minimal interaction with other medications. The approved dosing for postherpetic neuralgia of 3 patches for a maximum of 12 hours in a 24-hour period potentially limits its utility in DPN, for which there has been only a single case published of treatment with the 5% lidocaine patch. We herein report an open-label study of the 5% lidocaine patch in 56 patients with painful DPN and assess the safety and tolerability of a higher and more flexible dosing regimen.

METHODS

PATIENTS

The study protocol was approved by the institutional review boards of the 3 participating sites (Rochester, NY; Birmingham, Ala; and Jacksonville, Fla), and all patients provided informed consent. The inclusion criteria were presence of clinically defined painful DPN of at least 3 months' duration; an average daily pain diary rating for the baseline week of at least 4 on the Brief Pain Inventory (BPI) 0- to 10-point rating scale of average pain; at least 1 hour of moderate or severe pain on a verbal pain rat-
ing scale daily in the preceding 3 months; a stable analgesic drug regimen and dosages for at least 1 week before the baseline visit (although not a specific criterion, subjects receiving a tricyclic antidepressant had received stable dosages for >30 days); and a hemoglobin $A_1c$ level of no greater than 0.13% of total hemoglobin. Exclusion criteria were any other pain more severe than the painful DPN; open skin lesions in the area where the patches were to be applied; previous treatment with topical lidocaine; known hypersensitivity to lidocaine or amide anesthetics; current treatment with class I antiarrhythmic agents; history of excessive alcohol use or illicit drug use; and history of a suicide attempt or a current suicide intent or plan. Enrolled patients underwent assessment at baseline as having painful DPN either with or without mechanical allodynia.

PROCEDURE

Treatment consisted of the immediate daily application to the area of maximal DPN pain of up to 4 lidocaine patches (18 hours on and 6 hours off per day) for 3 weeks. Patches could be cut, and the application manner was at the subject's discretion; an attempt was made at each dosing period to cover the entire painful region with lidocaine patches. An increase in prior stabilization analgesic therapy or the introduction of new analgesics was not allowed during the study period. As specified in the protocol, patients at 1 of the 3 study sites were treated for an additional 5 weeks, during which taper of concomitant analgesic therapy was permitted while maintaining adequate pain control.

Patients completed the BPI average pain rating in a daily diary. Assessments were also conducted of the short-form McGill Pain Questionnaire (SF-MPQ) sensory, affective, total, and visual analog pain scales, BPI pain relief, sleep quality, BPI interference of pain on daily activities, Beck Depression Inventory (BDI) depression scores, and Profile of Mood States (POMS) mood scores. Blood was drawn at the screening visit and at the end of treatment week 3 to assess hemoglobin $A_1c$ levels. Samples for measurement of plasma lidocaine levels were drawn approximately 10 to 12 hours after the last patch application at the end of treatment weeks 1 and 3.

STATISTICAL ANALYSIS

The primary outcome variable was the change in mean daily pain diary ratings from baseline to week 3. Secondary outcome measures of change from baseline to week 3 and baseline to week 8 included the additional pain measures (SF-MPQ pain quality and intensity scales and BPI pain relief), the health-related quality-of-life (QOL) measures (sleep quality, pain interference, depression, and mood), and assessments of safety and tolerability.

We performed analyses on data from all patients for whom baseline and any postbaseline data were available. Final assessments were performed at the time of discontinuation for all patients who discontinued the study medication regimen prematurely for any reason. All patients were included in the safety analyses. Analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC). We used a 2-way repeated-measures analysis of variance with terms for visit (baseline vs week 3 or week 8) and patient group (allodynia [DPN$_a$] vs no allodynia [DPN$_{na}$]) to compare within- and between-group changes in outcome variables from baseline to week 3 in the total sample and from baseline to week 8 in the subgroup of patients allowed to taper concomitant analgesic therapy. The McNemar test was used for within-group comparisons of sleep quality. Analysis of adverse events was descriptive. Two-tailed $P<.05$ was considered statistically significant.

RESULTS

We enrolled 56 patients with painful DPN; 19 patients were in the DPN$_a$ group and 37 were in the DPN$_{na}$ group. Patients with DPN$_a$ and DPN$_{na}$ did not differ with respect to age, sex, ethnicity, or baseline pain intensity in the daily pain diary in independent-sample $t$ tests.

Significant improvement was found in the primary end point of change in mean daily pain diary ratings from baseline week to week 3, SF-MPQ total, sensory, affective, and visual analog scores, and BPI pain relief scores in the total sample of patients (Table 1 and Figure). Overall, 37 (70%) of 53 patients with week 3 pain ratings demonstrated a reduction of at least 30% in weekly mean daily pain diary ratings from baseline to week 3, including 13 (68%) of 19 patients with DPN$_a$ and 24 (71%) of 34 patients with DPN$_{na}$. Furthermore, 6 patients with DPN$_a$ (32%) and 17 patients with DPN$_{na}$ (50%) demonstrated a greater than 50% reduction in weekly mean daily pain diary ratings from baseline week to week 3.

Treatment was also accompanied by significant improvements from baseline to week 3 in the total sample
in sleep quality and all aspects of pain interference assessed by the BPI (Table 2). Significant improvement was also seen in Beck Depression Inventory depression scores and the Profile of Mood States tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, and total mood-disturbance scales in the total sample (Table 2). There were no significant interactions between visit and patient group in the repeated-measures analyses of variance, indicating that the patients in the DPN, and DPN_A groups did not differ in the extent to which they experienced improvement with treatment on any of the measures for which improvement was significant in the total sample of patients.

In the subgroup of patients who were treated for an additional 5 weeks, during which taper of concomitant analgesic therapy was permitted (n=28), 7 patients underwent taper of gabapentin, amitriptyline hydrochloride, or tramadol hydrochloride therapy. Three patients had complete discontinuation of concomitant pain medication therapy (2 of gabapentin and 1 of amitriptyline), and 4 patients maintained a reduced dosage, including 2 receiving gabapentin (50% and 67% reductions), 1 receiving tramadol (50% reduction), and 1 receiving amitriptyline (25% reduction). No patients required an increase in their concomitant pain medication dosages. In the entire subgroup, improvements in pain and QOL were maintained for all of the outcome measures at 8 weeks that had demonstrated significant benefits at 3 weeks in the complete sample except for SF-MPQ affective scores and sleep quality; in addition, vigor-activity was significantly improved in the subgroup at 8 weeks. In the 7 patients who underwent taper of concomitant medication dosages in this subgroup, significant improvements on daily pain diary ratings, SF-MPQ sensory and total scores,

Table 2. Quality-of-Life Outcome Measures*

<table>
<thead>
<tr>
<th>Measure</th>
<th>DPN Patients Baseline</th>
<th>DPN Patients Week 3</th>
<th>DPNNA Patients Baseline</th>
<th>DPNNA Patients Week 3</th>
<th>Total Sample Baseline</th>
<th>Total Sample Week 3</th>
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<tbody>
<tr>
<td><strong>Sleep quality</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Satisfactory/wake up refreshed, %</td>
<td>31.6</td>
<td>63.2</td>
<td>24.2</td>
<td>57.6</td>
<td>26.9</td>
<td>59.6‡</td>
</tr>
<tr>
<td><strong>BPI</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>General activity</td>
<td>3.8 (2.7)</td>
<td>2.4 (2.7)</td>
<td>4.5 (2.6)</td>
<td>2.4 (2.6)</td>
<td>4.3 (2.6)</td>
<td>2.4 (2.6)‡</td>
</tr>
<tr>
<td>Mood</td>
<td>3.3 (2.7)</td>
<td>1.9 (2.3)</td>
<td>3.7 (2.8)</td>
<td>2.0 (2.3)</td>
<td>3.5 (2.7)</td>
<td>2.0 (2.3)‡</td>
</tr>
<tr>
<td>Walking ability</td>
<td>4.7 (3.0)</td>
<td>4.3 (3.1)</td>
<td>6.3 (2.9)</td>
<td>4.8 (3.3)</td>
<td>5.7 (3.0)</td>
<td>4.6 (3.2)§</td>
</tr>
<tr>
<td>Normal work</td>
<td>4.5 (3.0)</td>
<td>3.3 (3.2)</td>
<td>5.1 (2.9)</td>
<td>3.8 (3.2)</td>
<td>4.9 (2.9)</td>
<td>3.6 (3.2)§</td>
</tr>
<tr>
<td>Relations with others people</td>
<td>2.3 (2.2)</td>
<td>1.4 (2.2)</td>
<td>2.8 (2.9)</td>
<td>1.6 (2.0)</td>
<td>2.7 (2.7)</td>
<td>1.5 (2.0)†</td>
</tr>
<tr>
<td>Sleep</td>
<td>6.2 (2.9)</td>
<td>3.8 (2.9)</td>
<td>6.4 (2.6)</td>
<td>3.5 (2.8)</td>
<td>6.3 (2.7)</td>
<td>3.6 (2.8)†</td>
</tr>
<tr>
<td>Enjoyment of life</td>
<td>4.6 (3.1)</td>
<td>2.4 (3.0)</td>
<td>4.7 (3.3)</td>
<td>2.7 (3.0)</td>
<td>4.7 (3.2)</td>
<td>2.6 (3.0)§</td>
</tr>
<tr>
<td>Summary score</td>
<td>29.5 (15.9)</td>
<td>19.5 (16.8)</td>
<td>33.5 (15.4)</td>
<td>20.8 (16.1)</td>
<td>30.2 (15.6)</td>
<td>20.3 (16.2)†</td>
</tr>
<tr>
<td><strong>BDI</strong></td>
<td>9.1 (5.5)</td>
<td>6.2 (5.0)</td>
<td>11.3 (7.2)</td>
<td>7.7 (6.1)</td>
<td>10.5 (6.7)</td>
<td>7.2 (5.7)‡</td>
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<tr>
<td><strong>POMS</strong></td>
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<td></td>
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<tr>
<td>Tension-anxiety</td>
<td>3.9 (5.2)</td>
<td>1.0 (3.9)</td>
<td>5.9 (7.6)</td>
<td>3.2 (6.3)</td>
<td>5.2 (6.8)</td>
<td>2.4 (5.6)‡</td>
</tr>
<tr>
<td>Depression-dejection</td>
<td>5.9 (5.6)</td>
<td>3.9 (5.2)</td>
<td>8.1 (9.7)</td>
<td>5.1 (6.9)</td>
<td>7.3 (8.5)</td>
<td>4.7 (6.3)§</td>
</tr>
<tr>
<td>Anger-hostility</td>
<td>4.3 (5.0)</td>
<td>2.4 (2.6)</td>
<td>6.3 (7.9)</td>
<td>4.8 (7.1)</td>
<td>5.6 (7.0)</td>
<td>4.0 (6.0)∥</td>
</tr>
<tr>
<td>Vigor-activity</td>
<td>17.1 (6.0)</td>
<td>18.4 (5.2)</td>
<td>14.5 (7.1)</td>
<td>15.7 (7.5)</td>
<td>15.5 (6.8)</td>
<td>16.7 (6.8)</td>
</tr>
<tr>
<td>Fatigue-inertia</td>
<td>9.4 (6.2)</td>
<td>6.4 (4.6)</td>
<td>11.9 (6.9)</td>
<td>9.5 (7.4)</td>
<td>11.0 (6.7)</td>
<td>8.4 (6.7)†</td>
</tr>
<tr>
<td>Confusion-bewilderment</td>
<td>0.8 (3.2)</td>
<td>0.4 (3.7)</td>
<td>2.0 (5.2)</td>
<td>0.9 (4.1)</td>
<td>1.5 (4.6)</td>
<td>0.7 (4.0)</td>
</tr>
<tr>
<td>Total mood disturbance</td>
<td>41.6 (18.2)</td>
<td>32.4 (14.3)</td>
<td>46.4 (27.8)</td>
<td>36.8 (21.4)</td>
<td>44.6 (24.6)</td>
<td>35.2 (19.1)†</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1; BDI, Beck Depression Inventory; POMS, Profile of Mood States.
*P values are calculated from a 2-factor repeated-measures analysis of variance model for continuous variables and from the McNemar test for the categorical variable of sleep quality.
†Unless otherwise indicated, data are expressed as mean (SD).
‡P<.001.
§P<.01.
∥P<.05.
BPI pain relief, and fatigue-inertia, but none of the other measures, were found at the end of this additional 5-week treatment period. Of the 56 patients enrolled, 1 withdrew before dosing and 4 withdrew secondary to adverse events during the 3-week study period (7.3%). Of these adverse events, 2 were deemed related to the study drug and consisted of application-site pain or burning. There were no systemic adverse events reported, and no serious adverse events occurred during the trial. Five patients reported burning sensations at the application site, 2 had pain exacerbation, 1 had a papular rash, and 1 had a photosensitivity reaction. The mean ± SD plasma lidocaine levels for the cohort did not differ significantly between the end of treatment weeks 1 (24.1 ± 19.7 ng/mL) and 3 (28.2 ± 23.0 ng/mL); these levels are well below lidocaine serum levels associated with an antiarrhythmic effect (1.5 µg/mL [6.4 µmol/L]) or toxicity (5.0 µg/mL [21.4 µmol/L]).

**COMMENT**

In this open-label trial, the 5% lidocaine patch significantly reduced pain and improved QOL in patients with painful DPN. Although regression to the mean and placebo effects cannot be ruled out, the beneficial response was consistent across all the measures, occurred in patients whether or not they had allodynia, and was maintained to 8 weeks of treatment. After 3 weeks of treatment, two thirds of patients demonstrated a reduction of at least 30% in the weekly mean daily pain diary ratings, a clinically important degree of pain relief. Few clinical trials of neuropathic pain have separated patients into those with and without allodynia. This distinction may not only be important in understanding the pathophysiology of neuropathic pain but also have ramifications for treatment. Nevertheless, there were no differences between the patients in the DPNa and DPNaA groups in the magnitude of their improvement in any of the pain and QOL outcome measures, suggesting that treatment with the 5% lidocaine patch may have comparable effectiveness in these 2 groups. It is important to emphasize, however, that allodynia can be caused by different pathophysiological mechanisms and that assessments of specific pain mechanisms may be associated with the treatment response.

A secondary objective of the study was to examine whether treatment with the 5% lidocaine patch reduced the negative impact of painful DPN on activities of daily living and psychological distress. We found significant improvements in all of the pain interference measures, 2 measures of depression, anger-hostility, fatigue-inertia, tension-anxiety, and total mood disturbance. A beneficial impact of treatment on QOL has not been uniformly demonstrated in analgesic clinical trials in patients with neuropathic pain. These results suggest that the generally excellent tolerability of the 5% lidocaine patch might translate to improvements in QOL that may be less likely to occur with more poorly tolerated treatments.

An additional objective was to determine the safety and tolerability in patients with DPN of 4 lidocaine patches with an application period of 18 hours on and 6 hours off. Data from a prior pharmacokinetic study in healthy patients demonstrated that application of 4 patches for 18 h/d yielded blood lidocaine levels that are safe, with an adverse event profile that was not appreciably different from that found when the dosage approved by the US Food and Drug Administration is used. The present regimen was selected because painful DPN manifests bilaterally in the lower extremities and is more severe at night. Application of 4 patches for 18 h/d makes it unnecessary for patients to cut patches to apply an equal number to both feet and allows patches to be applied for the entire night and most of the day. No significant adverse events were found in the present study with this regimen, and the results suggested that there is no systemic accumulation of lidocaine during a 3-week treatment period. The minimum drug concentrations in patients with DPN were similar to steady-state minimum drug concentrations previously reported in healthy volunteers who applied 4 patches for 18 h/d.

In conclusion, a more flexible dosing regimen of the 5% lidocaine patch was well tolerated, and the beneficial response suggests that it may be an effective treatment for the management of painful DPN. A double-blind, randomized, vehicle-controlled trial must be conducted to confirm our observations.
Michael Roura, MD, was the principal investigator for the Northeast Florida Endocrine Diabetes Associates, Jacksonville, Fla, study site. We thank Arnold R. Gammaitoni, PharmD, Jim Copp, PhD, and Napoleon Oleka, PhD, of Endo Pharmaceuticals for their invaluable assistance.

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REFERENCES

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