Incidence of Postherpetic Neuralgia After Combination Treatment With Gabapentin and Valacyclovir in Patients With Acute Herpes Zoster

Open-label Study

Whitney Lapolla, MD; Catherine DiGiorgio, MD; Kassie Haitz, MD; George Magel, MD; Natalia Mendoza, MD; James Grady, PhD; Wenzhe Lu, BS; Stephen Tyring, MD, PhD

Objective: To evaluate the efficacy of treatment with gabapentin plus valacyclovir hydrochloride for the prevention of postherpetic neuralgia in patients with acute herpes zoster.

Design: Uncontrolled, open-label study.

Setting: A private dermatology clinic.

Participants: Consecutive immunocompetent adults (age, ≥50 years) who presented with herpes zoster within 72 hours of vesicle formation with moderate to severe pain (≥4 on the 10-point Likert scale) were recruited for study participation.

Intervention: The patients received 1000 mg of valacyclovir hydrochloride 3 times a day for 7 days plus gabapentin at an initial dose of 300 mg/d, titrated up to a maximum of 3600 mg/d, side effects permitting.

Main Outcome Measures: Proportion of patients with zoster pain (pain >0) at 3, 4, and 6 months as well as average pain severity, the proportion of patients with sleep disturbance, and quality-of-life measures (determined by the Medical Outcome Study Short Form 36-Item Health Survey).

Results: A total of 133 patients (mean age, 64.6 years) were enrolled in the study. The overall incidence of zoster pain at 6 months was 9.8%.

Conclusion: The combination of gabapentin and valacyclovir administered acutely in patients with herpes zoster reduces the incidence of postherpetic neuralgia.

Trial Registration: clinicaltrials.gov Identifier: NCT01250561.


OSTHERPETIC NEURALGIA (PHN) is the painful sequela of acute herpes zoster virus infection described as burning or throbbing pain, sharp stabs, electric shocks, and allodynia.1 The time threshold after the clinical eruption of zoster for pain to be classified as PHN is variable (30, 90, or 120 days or 6 months) across researchers; however, recent models support 90 days as the most appropriate time point definition.2,3 Risk factors for PHN development include herpes zoster infection at older age, worse acute pain, more severe rash, and the presence of a painful prodrome.3,6 The cause of PHN is presumably nerve damage resulting from herpes zoster infection. Pathologic findings include primary afferent neuronal body and axon degeneration, atrophy of the spinal cord, scarring of the dorsal root ganglion, and loss of epidermal innervations.7,8 Postherpetic neuralgia is exceedingly difficult to treat and has been shown to cause severe impairment in quality of life similar to many other systemic diseases.9-12 Current therapies include tricyclic antidepressants, anticonvulsant agents, and a variety of oral and topical analgesics; however, these therapies are only partially effective in relieving pain.2 The primary goal for PHN management is to develop more effective treatment geared toward disease prevention rather than palliation.2 Several studies have demonstrated the efficacy of gabapentin for PHN.13-17

See Practice Gaps at end of article

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Author Affiliations: Center for Clinical Studies, Houston, Texas (Drs Lapolla, DiGiorgio, Haitz, Magel, Mendoza, and Tyring); Office of Biostatistics, University of Texas Medical Branch at Galveston (Drs Grady and Mr Lu); and Department of Dermatology, University of Texas Health Science Center at Houston (Dr Tyring).
nal studies suggest that gabapentin may be even more effective when prescribed for acute neurologic rather than chronic conditions.18 In a study of mice inoculated with the herpesvirus, the use of gabapentin reduced the incidence of PHN.19 A study in healthy volunteers demonstrated the efficacy of gabapentin therapy in preventing neuronal sensitization when capsaicin was subsequently applied.20 Multiple studies have demonstrated that preoperative gabapentin therapy reduces postsurgical acute pain by preventing central sensitization of dorsal horn neurons.21 This same approach may be reasonable when applied to acute herpes zoster. The purpose of this study was to evaluate the efficacy of gabapentin plus antiviral therapy for the prevention of PHN in patients with acute herpes zoster.

METHODS

PATIENT SELECTION

After approval was obtained from the University of Texas Health Science Center at Houston institutional review board, consecutive adult patients who presented with acute herpes zoster to the Dermatology Associates of Texas and the Center for Clinical Studies in Houston, Texas, between February 2002 and October 2007 were recruited for study participation. After completing an informed consent document, willing participants who satisfied inclusion and exclusion criteria (Table 1) were enrolled in the study. The study participants provided demographic data, including age, sex, and race, during the initial interview. Race/ethnicity was defined by the participants.

<table>
<thead>
<tr>
<th>Table 1. Inclusion and Exclusion Criteria for Study Participation</th>
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<tr>
<td><strong>Inclusion Criteria</strong></td>
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<tr>
<td>• Male or female patients 50 y and older</td>
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<td>• Patients with a clinical diagnosis of uncomplicated herpes zoster presenting within the first 72 h of vesicles</td>
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<tr>
<td>• Patients who are willing and able to comply with the requirements of the study</td>
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<tr>
<td>• Patients who are willing and able to give written informed consent</td>
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<tr>
<td>• Average pain score ≥4 on the 10-point Likert scale before therapy</td>
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</table>

PROTOCOL SUMMARY

All participants received 1000-mg caplets of valacyclovir hydrochloride, which were to be taken 3 times a day for 7 days. They also received gabapentin at an initial dose of 300 mg/d. The daily gabapentin dose (300 mg per capsule) was increased each week over 4 weeks in a stepwise manner (900, 1800, 2700, and 3600 mg/d divided 3 times a day), in accordance with patient tolerance and side effects, to a maximum total dose of 3600 mg/d. In patients who developed intolerable adverse effects, the dose of gabapentin was reduced by 1 level and continued at that level for the rest of the study. At the end of 4 weeks, gabapentin therapy was discontinued in those persons reporting mild pain (<4 on a Likert scale of 0-10) or no pain averaged over the duration of the previous week. Participants with an average pain score of 4 or greater were offered continued therapy with gabapentin for another 4 weeks at the maximum tolerated dose. After 4 or 8 total weeks, the dosage of gabapentin therapy was tapered over 1 week. No patient received gabapentin beyond week 9.

Patients took the first dose of the study drug in the presence of the investigators; therefore, all patients had at least 1 dose of valacyclovir and 1 dose of gabapentin. For this reason, the primary efficacy analysis was performed using all study patients. The primary study end points were presence of pain greater than 0 assessed at the 3-, 4-, and 6-month follow-up visits. Our calculations of PHN prevalence were based on the assumption that once zoster pain resolves it does not return; therefore, for all patients who reported 0 pain and were then unavailable for follow-up, the 0 was carried forward to future time points for statistical analysis. The proportion of patients with pain greater than 0 was also calculated without carrying 0s forward in time for all time points. Mean pain scores were reported for pain intensity. The preva-
In terms of pain at presentation, fewer patients with moderate and severe pain at weeks 12, 16, and 24 were patients reporting pain greater than 0 at week 12, 16, and 24 were 20.3%, 18.0%, and 9.8%. The percentages of patients with reported pain greater than 0 at final study visit: 6.8%.

The first reported visit with complete cessation of pain (7-10 on the 10-point Likert scale) was calculated. The timing of the first visit at which patients reported 0 pain was compared according to age, sex, and groups defined by the level of zoster pain (moderate and severe) at presentation. Secondary efficacy parameters of interest were quality-of-life measures, including sleep disturbance and numerical scores calculated from MOS SF-36 responses (physical and mental component summary measures).

Study end points were assessed for the study group as a whole and compared with historical data. Each end point was also assessed individually according to age group (50-59, 60-69, and ≥70 years), sex, and level of pain at presentation. Level of pain at presentation was categorized as moderate if pain was 4 through 6 on study day 1 and severe if pain was 7 through 10.

## RESULTS

### PATIENT DEMOGRAPHICS

A total of 133 patients met the criteria for enrollment in the study: 44 men (33%) and 89 women (67%). The mean patient age at the time of study enrollment was 64.6 years; 82% of the patients were non-Hispanic whites, 10% were Hispanic, 5% were African American, and 3% were Asian. According to initial pain at presentation, 38% of the patients complained of moderate pain (4-6 on the 10-point Likert scale) and 62% complained of severe pain (7-10 on the 10-point Likert scale) (Table 2). Thirty-seven patients were unavailable for follow-up before completion of the 6-month study; 15 of the 37 patients reported a pain level of 0 at their final study visit.

### INCIDENTAL OF PAIN AT WEEKS 12, 16, AND 24

The percentages of patients with reported pain greater than 0 at week 12, 16, and 24 were 20.3%, 18.0%, and 9.8%, respectively (Table 3). An alternative pain proportion calculation without assuming the durability of a reported 0 pain score resulted in proportions of patients with pain greater than 0 of 31.0%, 27.0%, and 13.5% for weeks 12, 16 (P = .06), and 24, respectively (Figure 1). In terms of pain at presentation, fewer patients with moderate pain at presentation had pain at weeks 12 (P = .50), 16 (P = .06), and 24 (P = .08) compared with patients with severe pain at presentation; the difference between the groups approaches significance when compared at static time points and reaches statistical significance (P < .01) when the proportion of patients with pain over the course of the study is examined using logistic regression (Figure 2). According to age group, a greater proportion of patients in the group of patients 70 years or older had pain at weeks 12, 16, and 24 compared with patients aged 50 to 59 years; the same outcome was found in patients aged 50 to 59 years compared with the 60- to 69-year-old age group. However, the difference in pain prevalence when patients are divided into age groups was not statistically significant (week 12, P = .20; week 16, P = .30; and week 24, P = .20). There was no statistical difference in the proportion of patients with persistent pain according to sex (P = .10). For the study group as a whole, the incidence of PHN (pain >3 at 90 days after zoster) was 6.8%.

### INITIAL VISIT WITH TOTAL PAIN CESSION

The first reported visit with complete cessation of pain was significantly different according to pain (P = .009) at presentation. For patients with severe pain at presenta-
portion of patients affected by sleep disturbance improved over time (Figure 5). There was no significant difference between sleep disturbance among age groups (P=.50) or initial pain severity (P=.20).

**COMMENT**

Acute herpes zoster infection leads to PHN in a subset of patients. Once PHN is established, the pain can be extremely difficult to manage; therefore, prevention of PHN is the ideal approach. The addition of gabapentin to valacyclovir therapy in our study group resulted in the lowest 6-month pain (>0) prevalence (9.8%) and incidence of PHN (6.8%) ever reported in a formal study, to our knowledge, albeit without a placebo control group; therefore, we relied on the literature for data comparison.

Citations in the literature report PHN prevalence from 9% to 73%; however, these numbers are not easily comparable given the varying definitions of zoster pain, the disparity in age groups (≥16, ≥18, ≥50, and ≥60 years), and the wide variety of pharmaceutical agents used. Our study included only the patients most likely to develop PHN: those of older age (≥50 years) with worse pain at presentation (pain ≥4 on the 10-point Likert scale). A chart containing the prevalence of zoster pain (pain >0) at 6 months in a number of prospective or randomized, double-blind studies with an antiviral agent (acyclovir, valacyclovir, famciclovir, or brivudine) was presented in a meta-analysis by Whitley et al’s (Table 4); the prevalence of zoster pain and PHN in our study was notably lower. Prior to this study, only a few interventions proved to reduce the incidence of PHN. The herpes zoster vaccine decreases the incidence of PHN by 66.5%. Anti-viral agents, including acyclovir, valacyclovir, and famciclovir, are approved for the management of acute herpes zoster. These agents shorten the duration of viral shedding, decrease the formation of new lesions, and accelerate healing; whether they affect the development of PHN is unclear. A study of 72 patients older than 60 years with acute herpes zoster who were treated daily with amitriptyline plus an antiviral agent had a lower incidence of pain at 6 months compared with those who were treated with an antiviral agent plus a placebo, but, to our knowledge, this association has not been further explored. Corticosteroids used at the time of acute herpes zoster infection have been proposed for PHN prevention; however, studies of acute corticosteroid use have demonstrated improvement in acute zoster pain and quality of life but no change in the rate of zoster pain resolution or incidence of PHN.

Gabapentin is an effective and Food and Drug Administration–approved therapy for the palliation of PHN; patients who are treated with gabapentin have lower pain scores and less sleep disturbance. Gabapentin is a structural analog of γ-aminobutyric acid that acts on the α2δ subunit of voltage-gated calcium channels to reduce neurotransmitter release. There is wide disparity in gabapentin dosing (300–3600 mg/d). The dosage of gabapentin therapy is increased until appropriate relief is accomplished or until adverse effects limit further escalation. Although gabapentin is widely used to treat...
chronic neuropathic pain, animal studies suggest that gabapentin may be more effective when administered during an episode of acute pain rather than after chronic pain develops.18 Use of gabapentin for herpes zoster has become a commonly prescribed acute therapy, although no controlled study has supported this practice, to our knowledge.43 Our study intended to determine whether gabapentin use acutely benefits patients in the long term, even after patients have stopped taking the gabapentin. None of our patients used gabapentin beyond 9 weeks; our primary study end points were assessed much later, at 3, 4, and 6 months. Therefore, the gabapentin therapy in our study did not mask PHN pain, it prevented PHN from developing.

Aside from pharmaceutical intervention, identification of risk factors for PHN may better enable more appropriate treatment of zoster in patients at higher risk. Sex as a risk factor for PHN has been reported and refuted in the literature4,44; it was not evident in our study. Well-established risk factors for PHN include

![Figure 4. Quality of life, as assessed by response to the Medical Outcome Study Short Form 36-Item Health Survey (MOS SF-36) calculations. A, Mental component summary (MCS) score and physical component summary (PCS) score for all patients. B, Mental component summary by age-group. C, Physical component summary by age group. D, Mental component summary according to level of pain at presentation. E, Physical component summary according to level of pain at presentation.](image)

![Figure 5. Proportion of patients with sleep disturbance over duration of study.](image)
Table 4. Prevalence of Zoster Pain (Pain ≥0) at 6 Months in Selected Clinical Trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients With Pain, %</th>
<th>Study Age Requirement, y</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study: valacyclovir hydrochloride, 1000 mg 3 times daily for 7 d, plus gabapentin</td>
<td>9.80%</td>
<td>≥50b</td>
<td>...</td>
</tr>
<tr>
<td>Acyclovir, 800 mg 5 times daily for 7 d, vs placebo</td>
<td>14 vs 13</td>
<td>≥60</td>
<td>McKendrick et al,19 1989</td>
</tr>
<tr>
<td>Acyclovir, 800 mg 5 times daily for 7 d, vs placebo</td>
<td>15 vs 13</td>
<td>≥16</td>
<td>Morton and Thomson,20 1989</td>
</tr>
<tr>
<td>Valacyclovir hydrochloride, 1000 mg 3 times daily for 7 or 14 d, vs acyclovir, 800 mg 5 times daily for 7 d</td>
<td>19.9 vs 19.3</td>
<td>≥50</td>
<td>Beutner et al,21 1995</td>
</tr>
<tr>
<td>Valacyclovir hydrochloride, 1000 mg 3 times daily for 7 d, vs valacyclovir hydrochloride, 800 mg 5 times daily for 14 d</td>
<td>19.9 vs 18.6</td>
<td>≥50</td>
<td>Beutner et al,21 1995</td>
</tr>
<tr>
<td>Famiciclovir, 500 or 750 mg 3 times daily for 7 d, vs placebo</td>
<td>Approximately 20 vs 40</td>
<td>≥18</td>
<td>Tyring et al,24 1995</td>
</tr>
<tr>
<td>Valacyclovir hydrochloride, 1000 mg 3 times daily for 7 d, vs famciclovir, 500 mg 3 times daily for 7 d</td>
<td>19 vs 19</td>
<td>≥50</td>
<td>Tyring et al,20 2000</td>
</tr>
<tr>
<td>Brivudin, 125 mg/d for 7 d, vs famciclovir, 250 mg 3 times daily for 7 d</td>
<td>11.3 vs 9.6c</td>
<td>≥50</td>
<td>Wassilew et al,33 2005</td>
</tr>
<tr>
<td>Brivudin, 125 mg/d for 7 d, vs acyclovir, 800 mg 5 times daily for 7 d</td>
<td>22.7 vs 43.5</td>
<td>≥50</td>
<td>Wassilew et al,33 2003</td>
</tr>
</tbody>
</table>

aAdapted from Whitley et al.2
bPatients presenting with mild pain (<4 on the 10-point Likert scale) were excluded from study participation.
cPain greater than 3 (on the 10-point Likert scale) at the 3-month follow-up visit.

Figure 6. Proportion of patients with pain at visit weeks according to severity of pain at initial presentation (moderate [A]; severe [B]) in current study group compared with historical data from meta-analysis by Whitley et al.4

In conclusion, more than 1 million persons in the United States will develop acute herpes zoster each year, and a large portion of this group will develop PHN. With better disease-modifying treatment, perhaps the severity and duration of PHN can be reduced. The addition of gabapentin to antiviral therapy in our study group resulted in low levels of zoster pain at 3, 4, and 6 months. Without a placebo control, it is impossible to confirm the benefit of acute gabapentin therapy; therefore, larger-scale blinded studies are necessary. In the meantime, gabapentin should be considered as an adjunct to antiviral therapy for acute herpes zoster management, particularly in patients at highest risk for PHN (older age, severe pain at baseline).

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Correspondence: Whitney Lapolla, MD, Center for Clinical Studies, 451 N Texas Ave, Webster, TX 77598 (wlapolla@ccstexas.com).

Author Contributions: Drs Lapolla, DiGiorgio, Haitz, Magel, Mendoza, and Tyring (principal investigator) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tyring. Acquisition of

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