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Postherpetic Neuralgia: Role of Gabapentin and Other Treatment Modalities

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Summary: Postherpetic neuralgia (PHN) is a chronic and painful condition that may occur after a herpes zoster infection. The frequency of PHN after untreated zoster varies widely. Age is the most important risk factor for development of PHN. The condition occurs in an estimated 50% of patients older than 50 years. The pain of PHN can be severe and debilitating and is frequently associated with allodynia. Although in most patients pain remits within the first year, it may persist for a lifetime. Tricyclic antidepressants (TCAs), topical agents, opioids, and gabapentin, a structural γ-amino butyric acid (GABA) analogue, are the only agents that have demonstrated efficacy in randomized clinical trials for treatment of both the shooting and the burning form of pain associated with PHN. TCAs are among the most commonly used classes of agents for treating PHN and are effective in a significant proportion of patients. However, various adverse events can limit treatment. These side effects tend to be more acute in the elderly, the population most likely to suffer from PHN. Topical agents have led to mild to moderate improvement in patients with PHN but are usually ineffective as monotherapy for this condition. Until recently, carbamazepine was the only antiepileptic drug evaluated for the treatment of PHN. Over the past few years, however, gabapentin has received increasing attention as a useful treatment for neuropathic pain. Gabapentin lacks significant drug–drug interactions and has a favorable safety profile, which makes it particularly useful for treatment of PHN. **Key Words:** Postherpetic neuralgia—Gabapentin—Herpes zoster.

HERPES ZOSTER

Infection with the varicella zoster virus (VZV) can result in systemic infection or in a localized infection known as herpes zoster (HZ) or shingles (1). Herpes zoster, with an annual incidence close to 0.3% (2), arises from reactivation of a latent infection in the sensory ganglia and leads to a characteristic vesicular rash in a dermatomal pattern. Usually pain precedes the rash by days to weeks (3), and the most commonly affected sites include the trigeminal ganglion (herpes zoster ophthalmicus) and the thoracic dermatomes (4,5). The rash usually disappears in an average of 3 weeks. Treatment with antivirals (acyclovir, famciclovir, or valacyclovir) reduces the duration of pain in acute HZ neuralgia (6) and might significantly reduce the time to pain relief when treatment with tricyclic antidepressants (TCAs) is instituted to treat postherpetic neuralgia (PHN) (7). Although treatment with steroids was not found to reduce the incidence of PHN (8,9), the value of antiviral treatment in this regard has not yet been settled (10–14). When added to antivirals, steroid treatment did not result in additional benefit (12).

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POSTHERPETIC NEURALGIA

PHN is a chronic painful condition that sometimes occurs after a zoster infection. Although most investigators confirm persistent pain for at least 3 months after healing of the characteristic rash before making this diagnosis, others have diagnosed PHN as early as 3 to 4 weeks after healing (15–17) or not until 6 months after healing (18). The frequency of PHN after untreated zoster has varied widely in different series, but a meta-analysis of 14 placebo-controlled clinical trials of acyclovir for acute zoster found that 22% of placebo-treated patients went on to develop this condition (19). The most important risk factor for developing PHN is age (20), with incidence estimates of 50% for patients older than 50 years and 75% for those above 65 years (2,4,21). Women are more commonly affected than men (22), which might be a reflection of the predominance of women in the older age group.

The pain of PHN can be quite severe and incapacitating and is described as lancinating, stabbing, shooting, or steady and burning, and is frequently associated with

allodynia. Although the pain remits in most patients within the first year, it can persist for years or even a lifetime. The duration of the pain is also age-dependent, with pain lasting more than 1 year estimated to occur in 22% of patients over 55 years and 48% of patients over 70 years (2,21).

Treatment of PHN: randomized clinical trials

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are among the most commonly used classes of drugs for treatment of PHN. The best response has occurred after treatment with adrenergically active antidepressants such as amitriptyline (23–26), desipramine (27), and maprotiline (26).

Five controlled crossover trials evaluating the efficacy of TCAs in the treatment of PHN have been conducted (23–27). Three of these trials were placebo-controlled (two evaluating amitriptyline and one desipramine) and the other two were comparative trials of amitriptyline vs. maprotiline in the first and amitriptyline vs. zimeldine in the other. A positive response was defined as one in which the pain relief was at least of moderate degree or in which the patient was not disabled by the pain at the maximal tolerated dose. These trials were relatively small, each enrolling a total of 15 to 58 patients. In the placebo-controlled trials, a positive response was experienced by 47–67% of patients during the amitriptyline phase compared with 5–8% during the placebo phase. In the comparative trials, a positive response was experienced by 44% and 60% of patients during treatment with amitriptyline compared with 18% and 7% of patients during treatment with maprotiline and zimeldine, respectively. In general, the sooner treatment was initiated, the better the overall response (28).

Although TCAs were effective in a significant proportion of patients, adverse events such as dry mouth, urinary retention, constipation, sedation, orthostatic hypotension and cardiac conduction block can be treatment limiting (29). These side effects tend to be most acute in the elderly population, the age group most likely to suffer from PHN. To minimize these effects, TCAs should be started at a low dose and titrated slowly. A starting dose of 10 mg at bedtime for elderly patients is recommended, with weekly increments of 10–25 mg. The usual daily effective dose is 25–150 mg given once a day at bedtime. The full therapeutic efficacy of TCAs might not be seen before 1 to 2 weeks and sometimes not before 4 to 6 weeks (30). They should be used with caution in the elderly and in patients with heart disease, narrow-angle glaucoma, or prostatism.

Topical agents

The efficacy of treatment with topical agents was also evaluated in PHN patients. Two randomized clinical trials found capsaicin to be effective for treatment of PHN. After 6 weeks of treatment, capsaicin-treated patients experienced a 15–30% mean improvement in pain on the visual analogue scale compared with a 1–5% improvement for patients receiving vehicle cream (31,32). A third trial reported capsaicin to be ineffective in this condition (33). Recent double-blind trials have shown that lidocaine gel and patch administered in a single session resulted in significant short-term partial relief of PHN pain (17).

Opioids

For patients with refractory pain, opioids are occasionally used. A double-blind trial in patients with PHN found that pain relief after treatment with 120 mg oral codeine did not differ significantly from that after placebo (35). A more recent study using a higher dose found that opioid treatment is effective in relieving the pain of PHN. In a single-center, randomized, double-blind, placebo-controlled crossover trial design, 50 patients were started on oxycodone or placebo and titrated over 4 weeks to tolerability up to a maximal daily dose of 60 mg (36). This was followed by crossover to the alternate treatment for 4 weeks with no intervening washout period. Other therapies for PHN were continued at unchanged dosages for the duration of the trial. Pain intensity and pain relief were assessed using daily diaries, visual analogue scales for pain intensity, and categorical scales for both pain intensity and pain relief. Data from 38 patients were included in the efficacy analysis. Compared with placebo, oxycodone produced statistically significant pain relief and lessening of pain intensity, as measured on both the visual analogue and categorical scales. Seventy-six percent of patients reported adverse events on oxycodone, including constipation, sedation, and nausea.

Opioid treatment is not widely accepted for treatment of chronic neuropathic pain, and should be reserved for refractory patients after other therapies have been exhausted.

Other treatments

Until recently, carbamazepine was the only antiepileptic drug (AED) evaluated for treatment of PHN. In the single randomized clinical trial, carbamazepine was found to be effective in treating the lancinating component but was ineffective against the steady and burning component of pain (37).

Although treatments such as calcium channel blockers (38) and mexiletine (39) have been anecdotally reported to be effective, their efficacy was never established in randomized clinical trials. For refractory patients, there is also anecdotal evidence supporting the use of anesthetic blockade and neurosurgical procedures.

GABAPENTIN AND THE TREATMENT OF PAIN

Gabapentin is a structural γ-amino butyric acid (GABA) analogue that is approved by the United States Food and Drug Administration as an adjunctive AED for seizures of partial onset in patients 12 years of age and older. Over the past few years, it has received increasing attention as a drug potentially useful for treatment of neuropathic pain. Anecdotal and open-label series reports have discussed its efficacy in a wide variety of painful conditions, including complex regional pain syndromes, trigeminal neuralgia, postherpetic neuralgia, and neuropathic pain of the head and neck (40–45). It was also found to be effective in reducing tactile allodynia, mechano hyperalgesia, and thermal hyperalgesia in a variety of animal models of neuropathic pain, including the chronic constriction injury model (46), the formalin and carageenan foodpad tests, the streptozotocin model, and a model of postoperative pain (47–50). Its mechanism of action in the treatment of pain is not yet well understood. The binding site of gabapentin, the α_2-Δ subunit of a voltage-dependent calcium channel, might be mechanistically important in the drug's antineuralgic activity, because these calcium channels are significant in the development of central sensitization following deafferentation.

USE OF GABAPENTIN FOR TREATMENT OF PHN: A RANDOMIZED CLINICAL TRIAL

The safety and efficacy of gabapentin for treatment of PHN were evaluated in a large multicenter, double-blind, placebo-controlled, parallel group, randomized, 8-week clinical trial (51). This section provides a synopsis of that study.

Subjects and methods

Subjects from 16 United States outpatient clinical centers participated in the study (51). A 1-week baseline period preceded a 4-week titration phase during which gabapentin was titrated up to 3600 mg daily or the maximal tolerated dose. This was followed by a 4-week fixed-dose period at the maximal tolerated dose (Fig. 1). Patients randomized to receive treatment with gabapentin were started at an initial dose of 300 mg/day. The maximal daily gabapentin dose was 900 mg, 1800 mg, 2400 mg, and 3600 mg at the end of weeks 1, 2, 3, and 4, respectively. Eligibility criteria included age (18 years or older) and pain of at least moderate severity, i.e., a minimum score of 40 mm on the Visual Analogue Scale of the Short-Form McGill Pain Questionnaire (SF-MPQ), and of at least 3 months' duration after disappearance of the zoster rash. Patients could be maintained on stable doses of a narcotic or a TCA for the duration of the trial.

Eligible patients who gave informed consent underwent physical and neurologic examinations and were instructed to complete diaries evaluating overall pain and sleep. A minimum of five visits was scheduled for each patient: initial enrollment and screening; randomization; and after 2, 4, and 8 weeks of study treatment.

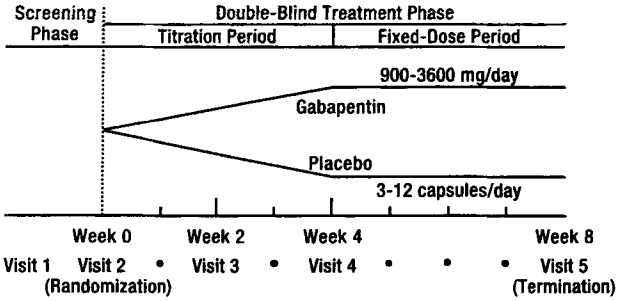


FIG. 1. Gabapentin for the treatment of post-herpetic neuralgia: a randomized controlled trial. Study design. Data from Rowbotham et al. (51).

During the second visit (1 week after baseline), patients completed the SF-MPQ, the Short-Form-36 (SF-36) Quality of Life Questionnaire, and the Profile of Mood States (POMS). Those patients who met the inclusion criteria and had completed at least four diaries were randomized to treatment with either gabapentin or placebo. Patients completed the SF-MPQ at weeks 2, 4, and 8, and the SF-36 and POMS at the final visit (week 8). In addition, patients completed the Subjects' Global Impression of Change Questionnaire and investigators completed the Clinical Global Impression of Change Questionnaire.

The primary efficacy parameter was the change in average daily pain score from the baseline week to the final study week, which was assessed from daily pain diaries and measured on a modified 11-point Likert scale (0 = no pain, 10 = worst possible pain) for the duration of the trial. Secondary efficacy parameters included changes from baseline in the following: average daily sleep rating score; the SF-MPQ total score, along with subscores for affective and sensory components of pain; the SF-36; and the POMS. Additional secondary efficacy parameters were present pain intensity (PPI) scores from the SF-MPQ, the Clinical Global Impression of Change, and the Subjects' Global Impression of Change. Measures of drug safety included the frequency and severity of adverse events.

Results

A total of 229 patients, mostly elderly individuals (median age 73 years), were randomized in the trial during the baseline visit (51). Of these patients, 184 (80.3%) completed the study, 15.3% discontinued the study because of adverse events, and 4.4% discontinued for other reasons. There was no significant difference between the active treatment and the placebo groups with respect to the percentage of patients who completed the study. Of

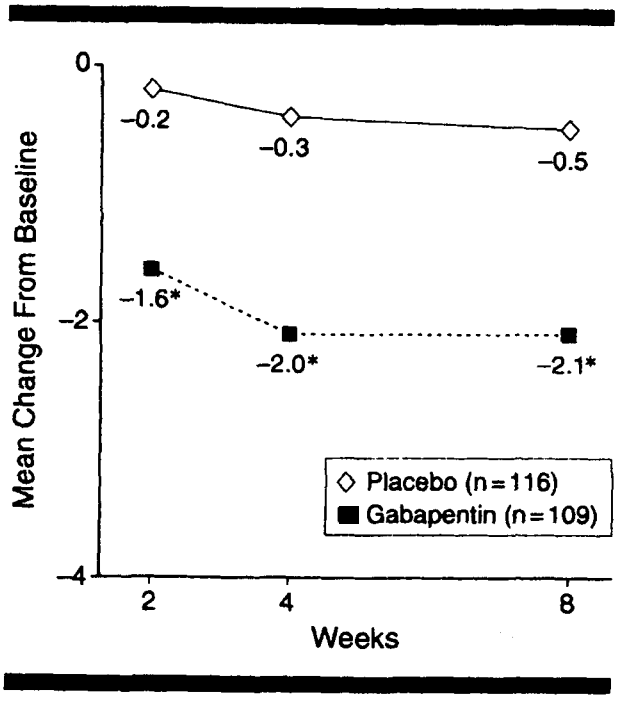
those patients treated with gabapentin who participated in the fixed dosing period, 83% received at least 2400 mg and 65% received 3600 mg gabapentin daily.

Primary efficacy analysis

The intent-to-treat analysis showed a statistically significant improvement in the average daily pain score in favor of the gabapentin-treated patients ($p < 0.001$) (51). For patients receiving gabapentin, the average daily pain score decreased by 33%, from a baseline value of 6.3 to 4.2 at the end of week 8. Placebo-treated patients had an 8% reduction in average daily pain scores, from 6.5 at baseline to 6.0 at week 8. These results represent a mean change from baseline of −2.1 (SD ± 2.1) and −0.5 (SD ± 1.6) in the gabapentin and placebo groups, respectively (Fig. 2). The pain reduction seen in the gabapentin group was already established at week 2, with a further reduction at week 4. At week 8, the reduction was maintained at the week 4 level. These end-of-study results were clinically significant.

Secondary efficacy analysis

Patients treated with gabapentin reported significant improvement in average daily sleep rating scores compared with those in the placebo group ($p < 0.001$) (51). In addition, for gabapentin-treated patients, mean SF-MPQ scores improved markedly for sensory pain ($p < 0.001$), affective pain ($p < 0.001$), and total pain ($p < 0.001$). Improvement in the SF-MPQ ratings of PPI was also statistically significant for patients treated with gabapentin ($p < 0.01$). At the conclusion of the trial, 16% of gabapentin-treated patients were pain free compared with 8.8% of patients treated with placebo.



*$p < 0.001$

FIG. 2. Change from baseline in average daily pain score (intent-to-treat analysis). Asterisk indicates $p < 0.001$. From Rowbotham et al. (51).

The Subjects' Global Impression of Change Questionnaire revealed that gabapentin provided a notable measure of pain relief for a large percentage of patients. A total of 43% of gabapentin-treated patients rated their pain as moderately or much improved at the end of the trial compared with baseline (categorical scale) vs. 12% of placebo-treated patients. The majority of patients in the placebo group (60%) reported no change in their level of pain compared with 23% of the gabapentin-treated subjects. The investigators' assessment was similar, as indicated by the Clinical Global Impression of Change Questionnaire.

The SF-36, which assessed physical functioning, role-physical, bodily pain, vitality, and mental health, all showed gabapentin to be superior to placebo ($p \leq 0.01$). In addition, patients treated with gabapentin showed significantly greater improvement in the POMS assessment of depression–dejection, anger–hostility, fatigue–inertia, confusion-bewilderment and total mood disturbance ($p \leq 0.01$) (51).

Safety and tolerability

The frequency, nature, and severity of adverse events were assessed in 229 patients, 113 of whom received GBP and 116 placebo (51). In this trial, gabapentin was well tolerated, with 13.3% of patients exiting because of side effects considered to be related to the study medication vs. 9.5% of placebo-treated patients.

There were no reports of serious adverse events determined by the investigator to be related to gabapentin treatment. Adverse events that occurred at a higher rate in the gabapentin group than in the placebo group were somnolence (27% vs. 5%), dizziness (24% vs. 5%), ataxia (7% vs. 0%), peripheral edema (10% vs. 3%), and infection (8% vs. 3%). The most frequent adverse event in the placebo group was pain, which occurred in 10.3% of patients compared with 4.4% in the gabapentin group.

In conclusion, the results of this study demonstrate that gabapentin is effective for reducing PHN pain, has a positive effect on sleep, quality of life, and mood, and is well tolerated.

As with TCAs, a low starting dose and a titration schedule will minimize the side effects that may occur with gabapentin treatment. A starting dose of 100 mg at bedtime is recommended for elderly patients. If tolerated, the dose can be increased to 300 mg at bedtime 2 or 3 days later, followed by 300 mg increments every 3–5 days until the patient experiences adequate pain relief. The usual effective daily dose ranges from 900 to 3600 mg administered tid.

SUMMARY

TCAs, topical agents, opioids, and gabapentin are the only drugs that have demonstrated efficacy for treatment of PHN in randomized clinical trials. In general, it is agreed that treatment with topical agents leads to mild or moderate improvement at best and is not effective as the sole therapy for this condition. TCAs have shown effectiveness in a large proportion of patients. However, anticholinergic and other adverse effects can limit tolerability. Conversely, lack of drug–drug interactions and an excellent safety profile make gabapentin very attractive for treatment of PHN. The results of an 8-week study confirm the efficacy of gabapentin in reducing PHN pain and demonstrate its beneficial effects on sleep, overall mood, and quality of life.

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