Managing Herpes Zoster and Postherpetic Neuralgia

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TREATMENT STRATEGIES FOR HERPES ZOSTER INFECTION INCLUDE LIMITING VIRAL REPLICATION WITH ANTI-INFECTIVE AGENTS AS WELL AS LIMITING ASSOCIATED ACUTE AND CHRONIC NEUROPATHIC PAIN WITH A VARIETY OF ANALGESICS. THE AUTHOR OUTLINES CURRENTLY AVAILABLE PHARMACOTHERAPEUTIC OPTIONS, FROM FIRST-LINE (EG, ANTI-INFECTIVE AGENTS, TRICYCLIC ANTIDEPRESSANTS, ANTICONVULSANTS, OPIOID ANALGESICS, AND TOPICAL AGENTS) THROUGH ADJUVANT TREATMENTS (EG, ORAL CORTICOSTEROIDS). A SUMMARY OF ADVERSE EVENT PROFILES IS PROVIDED FOR EACH MEDICATION. VACCINATION IS RECOMMENDED AS A PREVENTIVE MEASURE.

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Pharmacotherapy for herpes zoster should accelerate healing and reduce the severity and duration of associated pain. Postherpetic neuralgia (PHN) is defined along a continuum of pain—whether acute or chronic—and is measured from the onset of infection until final resolution.

Reducing the risk for complications is also important. Treatment strategies for zoster infection include limiting viral replication with antiviral agents and limiting acute and chronic pain with a variety of analgesics (Figure).1,2

Antiviral Agents
The first line of treatment and the most widely used agents for zoster infection are antiviral agents. As nucleoside analogs, they block viral replication.1,3

Antiviral agents accelerate healing in the acute phase of illness by shortening the duration of viral shedding as well as time to crusting and scabbing.2 In addition, they prevent new lesion formation.2 Pharmacotherapy with antiviral agents must be initiated within 72 hours of symptom onset (ie, rash) for maximum effectiveness. Any delay in administration may result in neuronal destruction—leading to the derangements of the central nervous system that are responsible for the neuropathic pain syndrome associated with PHN.

However, a course of therapy with an antiviral agent is recommended beyond the 72-hour window, especially in immunosuppressed patients as well as those with central nervous system disease.

Intravenous acyclovir may be administered to immunosuppressed patients 72 hours after rash onset. Acyclovir is initially phosphorylated by only the viral thymidine kinase; therefore, it is active only within cells infected with varicella-zoster virus (VZV). Cellular kinases metabolize the monophosphate to the triphosphate form, which acts as a competitive inhibitor of viral DNA polymerase.3

Placebo-controlled trials4-6 have demonstrated that oral acyclovir shortens the duration of viral shedding, halts the formation of new lesions, and accelerates the rate of healing, reducing the severity of acute pain.

A meta-analysis of data from these trials used the Kaplan-Meier method to...
determine that acyclovir was significantly more effective than placebo in the reduction of the duration of zoster-associated pain. The median time to pain resolution in the acyclovir-treated group was 41 days compared to 101 days in the placebo group. The proportion of patients receiving acyclovir with persistent pain at 6 months was 15% compared to 35% of patients receiving placebo.

Acyclovir has also been shown to reduce the percentage of eye disorders in cases of ophthalmic zoster from 50% to as much as 30%.

Malaise was the most frequent adverse effect with both acyclovir (11.5%) and placebo (11.1%). Adverse effects associated with intravenous acyclovir are local problems such as phlebitis or inflammation. Transient elevations in serum creatinine may also be observed.

Oral acyclovir has a limited oral bioavailability of 10% to 30%, which necessitates frequent dosing. The recommended dosing for oral acyclovir is 800 mg five times a day for 7 to 10 days. However, this regimen often proves challenging to adherence, especially among older patients reporting extreme discomfort.

Valacyclovir
Valacyclovir is the L-valyl ester of acyclovir. It is rapidly converted to acyclovir after oral administration and, in humans, results in three to five times greater bioavailability than that of acyclovir. The recommended dose of this medication is 1 g three times daily for 7 days, with each gram of valacyclovir yielding approximately 700 mg acyclovir and 300 mg of the essential amino acid valine.

In a randomized double-blind, placebo-controlled trial, researchers studied the safety and efficacy of oral valacyclovir vs oral acyclovir for the treatment of herpes zoster in 1141 immunocompetent adults. Three hundred eighty-four patients were randomly assigned to valacyclovir treatment for 7 days, 381 were randomly assigned to valacyclovir treatment for 14 days, and 376 were randomly assigned to treatment with acyclovir for 7 days. Seven- and 14-day valacyclovir regimens were used because the optimal duration of antiviral treatment for benefit against pain associated with herpes zoster had not been established at the time of that investigation.

Study results demonstrated that valacyclovir and acyclovir were equivalent in their rates of cutaneous healing, but valacyclovir treatment significantly accelerated pain resolution ($P=.001$ for 7-day treatment; $P=.03$, 14-day treatment). The median time to cessation of pain among study subjects was 51 days in the acyclovir treatment group compared to 38 days in the 7-day valacyclovir treatment group and 44 days in the 14-day valacyclovir group. No further advantage was observed with 14 days of valacyclovir treatment compared with 7 days of treatment.

On average, pain cessation was 34% faster with valacyclovir compared to acyclovir. At the end of the study, 19.3% of patients receiving valacyclovir reported continued pain, which was significantly lower ($P=.02$) than the proportion of patients in the acyclovir group with these symptoms (25.7%). Regardless of whether it is administered for 7 vs 14 days, valacyclovir had the same safety profile as acyclovir.

Famciclovir
Famciclovir is the diacetyl, 6-deoxy ester of penciclovir, which is a guanosine nucleoside analog. Metabolism of the prodrug to penciclovir begins with uptake by intestinal cells and is completed by the liver.

The current recommended dose is 500 mg three times daily. Famciclovir has been shown to accelerate zoster lesion healing and viral shedding. The median number of days to full crusting was 5 days in the famciclovir-treated group and 7 days in the placebo group. The median duration of viral shedding was 1 day in the famciclovir group and 2 days in the placebo group.

Importantly, there was an approximately twofold acceleration in the resolution of PHN in patients receiving famciclovir compared to those receiving placebo. The median duration of PHN was 63 days in the famciclovir group and 119 days in the placebo group, resulting in an overall reduction in symptom dura-
tion of approximately 2 months.\textsuperscript{12} Famiciclovir has a bioavailability of approximately 77\%, which is much higher than the 10\% to 30\% oral availability of acyclovir. The active triphosphate form of penciclovir has an intracellular half-life of 9.1 hours in VZV- and herpes simplex virus (HSV)-infected cells compared to the 1-hour half-life of acyclovir. Therefore, famciclovir may be administered at a lower dose and less frequently than acyclovir without compromising efficacy.

Famiclovir at 250 mg three times daily for 7 days was as effective as—and had a more favorable safety profile than—acyclovir at a dosage of 800 mg five times daily for 7 days. Moreover, famciclovir at a dose of either 750 mg once daily or 500 mg twice daily plus 250 mg once daily is as effective as acyclovir at 850 mg five times daily.\textsuperscript{13} Thus, famciclovir is as effective as acyclovir when administered only once a day, a regimen that encourages better patient compliance.

The efficacy and safety of famciclovir were directly compared to the efficacy and safety of valacyclovir in a double-blind randomized controlled multicenter clinical trial.\textsuperscript{14} Five hundred ninety-seven patients aged 50 years or older received 7 days of treatment with either valacyclovir 1 g three times daily or famciclovir 500 mg three times daily and were observed for 24 weeks.\textsuperscript{14} Intent-to-treat analysis did not detect a statistically significant difference between valacyclovir and famciclovir treatment based on the resolution of zoster-related pain. The proportion of patients with pain symptoms or after rash healing was 86\% for the valacyclovir group and 87\% for the famciclovir group. Sixty-four percent of patients in the valacyclovir group and 62\% in the famciclovir group had pain at 1 month after rash healing. Thirty-two percent and 34\% of the valacyclovir and famciclovir groups, respectively, reported continued pain at 3-month follow-up. At 6 months, 19\% in each group reported pain.

Valacyclovir and famciclovir had the same impact on rash healing. After 7 days, the rash was considered 100\% crusted or healed in 32\% of valacyclovir recipients and 25\% of famciclovir subjects. The rash was observed to have healed in 89\% and 82\% of valacyclovir and famciclovir recipients after 14 days and in 96\% and 99\% of valacyclovir and famciclovir recipients, respectively. Both drugs also had a similar safety profile.

Thirty-four percent of valacyclovir subjects and 38\% of famciclovir recipients reported at least one adverse event. Headaches, nausea, and gastrointestinal disturbances occurred more often in patients receiving valacyclovir or famciclovir than in patients receiving placebo.

Limitations of Antiviral Agents

When administered in the acute phase of illness, antiviral agents accelerate healing by 1 to 3 days. Not only do they shorten the duration of viral shedding, they reduce the time to crusting and scabbing and help prevent new lesion formation. They also accelerate the resolution of acute pain (ie, pain reported between days 1 and 30).

Although the effects of valacyclovir and famciclovir treatment on patients with ophthalmic zoster have not been studied to date, acyclovir has been shown to reduce the incidence of eye disorders in this population.

Antiviral agents have proven effective and safe in the pharmacologic management of herpes zoster infection, but some limitations are associated with these agents.\textsuperscript{3} As stated previously, therapy must be initiated within 72 hours of rash onset for maximal effectiveness. Regrettably, prompt recognition and treatment occur in fewer than 50\% of cases because of delayed physician consultation. In such situations, the effectiveness of antiviral agents is limited because they reduce lesion formation and time to crusting by only a few days. Last, while they may reduce the duration of PHN, they do not function prophylactically.

Oral Corticosteroids

As an adjuvant option in the treatment of patients with acute zoster infection, oral corticosteroids have been shown to ameliorate the inflammatory features of this condition, cosmetically improving the rash.

Five controlled trials have evaluated the effectiveness of corticosteroids in reducing the inflammatory features of zoster and preventing subsequent injury.\textsuperscript{3} Disparate results were observed, with a benefit noted in two trials\textsuperscript{15,16} but no benefit shown in another two.\textsuperscript{17,18} In the fifth trial,\textsuperscript{19} 208 adults aged 50 years old or older were given placebo or treated with high-dose prednisone alone, acyclovir alone, or acyclovir plus prednisone for 21 days. Results of this trial demonstrated that the acute neuritis resolved significantly (P<.05) earlier in the prednisone group than in other treatment groups, with a shorter period of analgesic treatment required and an earlier resumption of normal sleeping patterns and activity. Prednisone had no effect on PHN.

The use of oral corticosteroids in the treatment of patients with zoster infection is controversial, however. Those who are in favor of using corticosteroids recommend them because of the ability of this drug class to reduce the pain associated with the inflammatory aspect of zoster. Those who oppose the use of corticosteroids believe that, when used as an adjuvant to antiviral agents, corticosteroids provide limited additional benefit. Moreover, oral corticosteroids have been shown to reduce acute pain but not the chronic pain associated with PHN. Finally, corticosteroids are associated with upper gastrointestinal adverse events such as dyspepsia, and they have been shown to exacerbate diabetes, hypertension, and osteoporosis.\textsuperscript{20} These adverse effects are especially undesirable among older patients, the majority of individuals in whom zoster infection is diagnosed.

Pharmacotherapeutic Options for Postherpetic Neuralgia

An important element in the treatment of patients with zoster infection is management of the chronic pain associated with this condition. Treatment strategies for chronic pain must be tailored to each patient, as the symptoms of PHN can be unique to each patient.

Treatment goals include alleviating the pain associated with PHN and improving quality of life, allowing the patients to maintain sleep, physical activity, and nutrition. Tricyclic antidepressants (TCAs), anticonvulsants, opioid analgesics, and topical agents are recommended first-line therapies for PHN.
Tricyclic Antidepressants

Tricyclic antidepressants were the first agents to demonstrate efficacy in randomized controlled trials for PHN management and were considered first-line therapy for many years. Tricyclic antidepressants represent the most comprehensively studied class of drugs for the disorder. They block the reuptake of norepinephrine and serotonin. Thus, they may relieve pain by increasing the inhibition of spinal neurons involved in pain perception. Animal studies have shown that TCAs also may work as sodium channel antagonists within the peripheral nervous system, another mechanism that may be responsible for pain relief.

Results of six clinical trials, five of which evaluated amitriptyline hydrochloride, demonstrated that 47% to 67% of patients reported moderate to excellent relief.21 Amitriptyline was found to be superior to lorazepam, and nortriptyline hydrochloride, a metabolite of amitriptyline, was also found to be effective in ameliorating the pain associated with PHN. However, physicians prefer nortriptyline to amitriptyline because the former has fewer anticholinergic effects.

Adverse events associated with TCAs, which are mainly due to anticholinergic effects, include sedation, confusion, urinary retention, dry mouth, blurred vision, postural hypotension, and arrhythmia.21 These adverse events limit the usefulness of TCAs for treating older patients.22 Research continues to focus on discovering more effective treatment strategies for PHN.

Anticonvulsants

Two anticonvulsants are indicated for the treatment of PHN. Gabapentin, a structural analog of γ-aminobutyric acid, was approved by the US Food and Drug Administration in 2002 while pregabalin, an α-2δ ligand, received approval in 2005. It has been suggested that either anticonvulsant may be initiated in the acute phase of illness because the pathologic process that causes PHN begins during this phase and much of the neuronal damage has occurred before the pain is manifested.

Anticonvulsants are believed to work in neuropathic pain syndromes because they are involved in membrane stabilization, which reduces neuronal derangement.23,24

Although gabapentin’s mechanism of action is currently unknown, it appears to be independent of γ-aminobutyric acid receptors. It is lipophilic and penetrates the blood-brain barrier. Gabapentin’s analgesic effect was first documented preclinically in several rat models,25-28 including those with chronic neuropathic pain.

A large multicenter double-blind placebo-controlled trial23 investigated the effectiveness of gabapentin for alleviating the pain associated with PHN. Patients’ subjective measures of pain were reduced by 33% at the end of the study compared to a 7.7% pain score reduction in the placebo group. According to patient responses to the Global Impression of Change Questionnaire, 43.2% of subjects treated with gabapentin categorized their pain as “much” or “moderately” improved at the end of the study, whereas only 12.1% in the placebo group did so. In fact, on trial completion, 16% of gabapentin-treated subjects included a rating of “no pain” according to subjective measures of present pain intensity using the Short Form McGill Pain Questionnaire.23 In comparison, 8.8% of control subjects reported no pain at the conclusion of the study. Adverse events that occurred more frequently in the gabapentin group compared to those in the group receiving placebo were somnolence, dizziness, ataxia, peripheral edema, and infection.23

Pregabalin was initially reported effective in alleviating neuropathic and nociceptive pain in a variety of animal models. In a multicenter parallel-group double-blind randomized placebo-controlled trial, 63% of subjects receiving pregabalin reported a reduction in pain of 30% or more, as opposed to 25% of placebo controls (P=.001). Dizziness and somnolence were the most common adverse effects associated with pregabalin treatment, but they were tolerated by most patients.23

Opioid Analgesics

Many patients with PHN do not experience a clinically significant reduction in symptoms with TCAs or anticonvulsants. Opioids are an important option for this patient population. Opioids may also be initiated during the acute phase of illness when pain is moderately severe.

The opioid analgesics morphine and methadone were found to be as effective as the TCAs nortriptyline or desipramine in a randomized double-blind placebo-controlled crossover trial.29 A 50% decrease in PHN with controlled-release oxycodone hydrochloride at 45 mg per day was observed in another placebo-controlled trial.30 Intravenous morphine sulfate infusions have been shown to be effective in reducing the pain and hyperalgesia of PHN.21,31 In a longitudinal study on the use of oxycodone or morphine, 16 of 20 patients had continued reduction of pain at 6 months of treatment.21

Because individuals vary in their tolerance to opioids, doses must be titrated accordingly for each patient. Adverse events observed with opioids are minimal and include constipation, nausea, loss of appetite, dizziness, and drowsiness.21 A theoretical limitation to the use of opioids is the potential for addiction.

Topical Treatment

Among patients with PHN, especially those for whom PHN manifests peripherally, topical therapy is a viable treatment option. Such incidents are presumably due to ectopic discharge within cutaneous nociceptive afferents after VZV insult.

Topical treatment is also a good therapeutic option for patients in whom systemic treatment is contraindicated. Topical treatment is currently divided into three groups: combined aspirin and nonsteroidal anti-inflammatory drug (NSAID) formulations, local analgesics, and capsaicin cream.

Topical Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs applied topically are useful in treating patients with zoster during the active and early postherpetic phase of illness because pain symptoms are associated with tissue trauma and inflammation as well as an increased level of tissue prostaglandins.

Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase, decreasing
the synthesis of prostaglandins. Thus, there has been a recent focus on developing topical NSAIDs, such as powdered aspirin in chloroform or ethyl ether, to treat patients for PHN.

Over-the-counter creams and topical indomethacin, diclofenac, and benzoylamine hydrochloride cream have also been investigated for their pain-alleviating properties in PHN. Topical aspirin has been shown to be superior to placebo in reducing PHN, while other topical creams such as indomethacin, diclofenac, and benzoylamine, have not.21

**Analgesics**

A topical lidocaine 5% patch is a targeted peripheral analgesic that is indicated for the treatment of patients with PHN. When four patches were applied for up to 24 hours, the systemic absorption of lidocaine from the patch was minimal in healthy adults and even lower among patients with PHN, thus eliminating adverse systemic events.22

Vehicle-controlled and open-label trials found the lidocaine 5% patch, alone or in combination with other agents, effective in the treatment of patients for PHN. Sixty percent efficacy has been observed in pain relief with this patch.

Most adverse events reported were localized at the application site. Because of this proven efficacy and safety profile, the lidocaine 5% patch has been recommended as a first-line therapy for the treatment of neuropathic pain associated with PHN.22

**Capsaicin**

Capsaicin cream is also indicated for the treatment of patients with PHN.23 At high concentrations, capsaicin depletes substance P, a principal peptide neurotransmitter. This depletion first causes a burning sensation, then anesthetic effects.

In a controlled trial33 that involved 143 patients with PHN of at least 6 months’ duration, 61% of subjects in the capsaicin group reported a burning sensation on application of the cream, while only 33% of those in the placebo group did. After 4 weeks of treatment, there was a 21% reduction in the subjective pain score among capsaicin subjects, while there was only a 6% reduction in this measure among control subjects (P<.05).

Investigators remain skeptical about the use of capsaicin because of the initial burning sensation, which was deemed “intolerable” by up to one third of patients. Moreover, this burning sensation renders blinded studies virtually impossible.

**Comment**

Antiviral agents and oral corticosteroids are used in the treatment of patients with acute zoster infection. Over-the-counter creams and ointments may be used to alleviate the topical itching and burning associated with the rash. Antiviral agents are widely used, while the use of oral corticosteroids is controversial owing to their production of undesirable adverse events and their ineffectiveness in pain reduction. While neither antiviral agents nor oral corticosteroids reliably prevent PHN, the former may shorten the duration of PHN and the severity of the pain.

Tricyclic antidepressants and anticonvulsants are used in the treatment of PHN, with anticonvulsants being preferred owing to their more favorable adverse event profile. Topical agents such as topical NSAIDs, lidoderm, and capsicain cream are also used in the management of PHN, with topical NSAIDs being the least effective. Postherpetic neuralgia is difficult to treat because most of the neuronal damage that causes the chronic pain occurs during the acute phase of infection. Prevention being superior to cure, the most effective means of preventing PHN is to prevent zoster infection through vaccination.

**References**


