Herpes Zoster

Antivirals and Pain Management

Deborah Pavan-Langston, MD, FACS

Topic: Evaluation of evidence-based strategies for managing herpes zoster (HZ) and the pain of postherpetic neuralgia (PHN).

Clinical Relevance: Approximately 20% of the world's population suffers from herpes zoster at least once in a lifetime, with 10% to 20% having ophthalmic involvement. Treatment of the acute disease with oral antivirals may reduce the incidence and severity of complications but does not reliably prevent PHN or postherpetic itch (PHI). The acute pain abates as the acute phase resolves; the long-term pain of PHN or PHI may be severe and difficult to manage. Although many therapeutic agents have efficacy in the management of these complications, relief is frequently partial for months to the remainder of the lifetime.

Methods: Literature review was performed using the resources of the Harvard Medical School/Massachusetts Eye and Ear Infirmary Ophthalmic library as well as the National Library of Medicine and the National Institutes of Health PubMed service searching by pertinent topics, authors, and journals.

Results: If started within 72 hours of the onset of the acute HZ rash, the oral antiviral agents acyclovir, valacyclovir, and famciclovir significantly shorten the periods of acute pain, virus shedding, rash, acute and late-onset anterior segment complications, and, in the case of valacyclovir and famciclovir, the incidence and severity of PHN. However, these medications do not prevent PHN, which remains a common and debilitating complication of HZ in older patients, requiring assiduous pain management. Tricyclic antidepressants, antiseizure drugs, opioids, and topical analgesics all offer some pain relief, and may be combined.

Conclusion: Options are available to manage HZ and reduce the pain of PHN. However, prevention, now possible with the HZ vaccine, is preferable to treatment. *Ophthalmology 2008;115:S13–S20 © 2008 by the American Academy of Ophthalmology.*

Herpes zoster (HZ) is the result of reactivation of varicella-zoster virus (VZV) infection[1]; HZ ophthalmicus (HZO) arises when a latent infection of the trigeminal ganglion becomes reactivated and involves the ophthalmic division of its peripheral nerves.[2] It is estimated that between 10% and 20% of HZ cases have ophthalmic involvement, and of these cases, approximately 20% to 70% will have ocular involvement.[3,4] Herpes zoster ophthalmicus is more likely to occur in older than younger patients who have HZ.[3]

Herpes zoster itself typically presents as a rash, which, though itchy and painful, is of limited duration. However, some patients may develop further complications that can have a long and pernicious disease course. Ocular complications are generally painful and often chronic and can, in some cases, threaten the patient's sight.[2] In addition, patients with HZO run an even greater risk of developing postherpetic neuralgia (PHN), persistent neuropathic pain that lasts long after the initial rash has healed.

Aggressive management of acute HZ with antiviral medication can reduce the duration and severity of the acute zoster and, in the case of ophthalmic zoster, prevent more serious complications. Some antivirals may also reduce the severity or duration of PHN, although none have been reliably shown to prevent it.

The pain of PHN can be managed with tricyclic antidepressants (TCAs), anticonvulsants such as gabapentin or pregabalin, opioids, and topical analgesics. These treatments, which can be used in combination, offer some pain relief to patients, although this relief is often incomplete. Many cases of HZ and PHN can be prevented through vaccination. However, in those patients for whom vaccination is too late and for those who develop HZ despite vaccination, aggressive and early use of antivirals is key to attenuating the disease course.

Acute Herpes Zoster: Antivirals and Corticosteroids

Antivirals

Of the 20 Food and Drug Administration (FDA)–approved antiviral drugs, systemic acyclovir, valacyclovir, and famciclovir are the 3 with greatest clinical use in treating HZ. All 3 are FDA approved for use in herpetic disease.

Acyclovir (Zovirax, GlaxoSmithKline, Research Triangle Park, NC). Acyclovir [9-(2-hydroxyethoxymethyl) guanine], a second-generation antiviral drug, is a synthetic

From Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts.

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Correspondence to Deborah Pavan-Langston, MD, FACS, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114. E-mail: deborah.langston@meei.harvard.edu.

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purine nucleoside guanine analog.[5–7] The conversion of acyclovir to acyclovir monophosphate occurs mainly via virus-coded thymidine kinase and subsequently to a triphosphate via other cellular enzymes. The viral DNA polymerase has a 10- to 30-fold or greater affinity in vitro for acyclovir triphosphate than does the cellular α-DNA polymerase. When the acyclovir analog enters the viral DNA chain, DNA synthesis is terminated, thus abolishing viral protein synthesis. Acyclovir is phosphorylated so minimally by host cell enzymes that it is essentially nontoxic whether given systemically or topically.[5–7] Infrequent to rare side effects of oral acyclovir include diarrhea in lactose-intolerant patients, headache, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.[5,8]

Studies by Hung et al and Collum et al on the concentrations of acyclovir in the tear film and aqueous humor in patients on 400 mg (peroral 5 times daily) showed levels of 0.64 μmol/l (range, 0.16–1.45) and 3.26 μmol/l (range, 1.10–5.39), respectively, 4 hours after the last oral dose.[9,10] The mean effective dose of herpes simplex virus 1 (HSV-1) reducing viral plaque count in tissue culture by 50% ranges from 0.1 to 1.6 μmol/l, indicating that the tear film and aqueous levels achieved were well in excess of those needed to eliminate the virus. In comparison to those for HSV, the inhibitory doses for VZV are much higher, at 3 to 4 μmol/l, resulting in the need for 4-fold higher drug dosing, as noted above, and less leeway in terms of resistance.[11] To inhibit most strains of VZV, oral dosing of 800 mg 5 times a day is needed to yield peak and trough serum levels of 6.9 μmol/l and 0.96 μmol/l.[9,12,13]

Because of the high complication rate in HZO, several studies have been conducted comparing acyclovir with a placebo or other antiviral therapy. Acyclovir (600 or 800 mg peroral 5 times a day for 7 to 10 days) induces prompt resolution of rash and pain, induces more rapid healing, and reduces the duration of both viral shedding and new vesicle formation. Equally important, there is also a significant reduction in the incidence and severity of acute dendritiform keratopathy; incidence, but not severity, of corneal stromal immune keratitis; and incidence of late-onset ocular inflammatory disease (e.g., episcleritis, scleritis, iritis).[14–18] Dosing and time to treatment are key factors in treatment success. When adequate treatment of acyclovir was given (800 mg 5 times a day for at least 7 days starting within 3 days after rash eruption), complications occurred in only 4% (2/48) of patients; patients with no treatment or with inadequate treatment had a greater frequency of severe ocular complications: 21% (34/164) and 25% (5/20), respectively.[17] The effect on PHN varied, with some reports showing no efficacy and others demonstrating a notable decrease in severity and incidence in some patients. As will be discussed below, both famciclovir and valacyclovir are statistically superior to acyclovir in their effect on PHN.

Acyclovir-resistant HSV and VZV mutants are rarely seen in immunocompetent patients; however, resistant strains are being encountered ever more frequently in immunodeficient patients.[19,20] Systemic vidarabine and foscarnet are reasonable alternative drugs as they do not require thymidine kinase for activation.[21–24]

Valacyclovir (Valtrex, GlaxoSmithKline). Valacyclovir, a third-generation antiviral, is the L-valine ester and prodrug of acyclovir. This synthetic prodrug has greatly enhanced absorption from the gastrointestinal (GI) tract and is subsequently hydrolyzed to acyclovir. The bioavailability of acyclovir is enhanced 3 to 5 times via this prodrug and is not altered by the simultaneous administration of food.[25–27] A 1-g dose of valacyclovir produces peak plasma concentrations of 5 to 6 μg/ml of acyclovir, a therapeutic dose for both HSV and VZV. Valacyclovir (1 g 4 times daily) presents a concentration–time curve of acyclovir that is similar to that achieved with the intravenous administration of acyclovir (5 mg/kg of body weight every 8 hours).[27]

In an observational study of 1897 acute HZ patients treated with open-label valacyclovir (1 g peroral thrice daily for 7 days), 11% of whom had HZO, no difference was seen in drug effect on HZO versus HZ of other dermatomes (median duration of pain, 18 vs. 16 days, respectively). However, in subjects with HZO, abnormal sensations persisted significantly longer than in those with HZ at other sites (47 vs. 22 days, respectively).[28] A masked study of acute HZO comparing the efficacy of valacyclovir with that of acyclovir in 110 immunocompetent patients reported similar incidences of complications in both groups: conjunctivitis (54% with valacyclovir vs. 52% with acyclovir), punctate keratitis (39% with valacyclovir vs. 48% with acyclovir), dendritic keratitis (11% with both drugs), stromal keratitis (13% with both drugs), and uveitis (13% with valacyclovir vs. 17% with acyclovir). At 1-month follow-up, 25% of patients receiving valacyclovir and 31% of patients receiving acyclovir still had pain (not significantly different).[29] Neither group had incidence of neurotrophic keratitis or scleritis. It was concluded that valacyclovir was a valid alternative to acyclovir in treatment of HZO but, like famciclovir (discussed below), was superior in terms of patient compliance, requiring only thrice daily dosing.

Several clinical studies in immunocompetent patients with acute zoster have found that valacyclovir (1000 mg peroral thrice daily) offers efficacy equivalent to that of acyclovir (400 mg peroral 5 times daily).[30] A large masked study comparing valacyclovir (1 g peroral thrice daily) with acyclovir (800 mg peroral 5 times daily) in 1141 immunocompetent zoster patients (35 with HZO) followed for up to 1 year found that the drugs were equivalent in their ability to accelerate dermal healing and reduce the duration of viral shedding but that valacyclovir was significantly better in terms of acute pain resolution and reduced duration of PHN. No difference was seen between patients who received drugs for 7 versus 14 days.[30] Further, studies of PHN revealed that the median time to pain resolution was shorter among patients receiving valacyclovir than among those receiving acyclovir (38 vs. 51 days, $P<0.03$). Other studies support the major efficacy of valacyclovir in HZ rash resolution and superior inhibition of PHN, particularly if started within 72 hours of rash onset. Studies comparing valacyclovir (1500 mg peroral twice daily vs. 1000 mg peroral thrice daily) revealed that in patients older than 50 years cessation of pain was 43 days in the twice-daily group and only 23 days in the thrice-daily group, indicating that the drug was more effective at more frequent dosing.[27,31–37]

Central neurologic toxicity may be observed with high doses of valacyclovir but regresses when the drug is with-

drawn.[38] It is of note, however, that some severely immunocompromised human immunodeficiency virus patients have developed thrombocytopenic purpura/hemolytic uremic syndrome, including a few deaths.[39] As a result, this drug is not FDA approved for use in immunocompromised patients, but is approved for treatment of herpes zoster and genital HSV.

Famciclovir (Famvir, Novartis Pharmaceuticals Corp., East Hanover, NJ). Famciclovir, a third-generation nucleoside, is the orally bioavailable diacetyl ester of the active antiviral penciclovir. It is similar to acyclovir in mechanism of action and antiviral activity against HSV-1, HSV-2, and VZV but, like valacyclovir, is superior in GI absorption: 77%, versus only 30% for acyclovir.[40–42] The intracellular activity of penciclovir is very long, even when extracellular titers are low: 9 hours in zoster-infected cells compared with <1 hour for acyclovir triphosphate in similarly infected cells. Further, penciclovir triphosphate, a nonobligate DNA chain terminator, is more effective than acyclovir triphosphate, an obligate chain terminator, in inhibiting HSV DNA polymerase-mediated DNA chain elongation.[43,44] The drug is FDA approved for treatment of HZ infection at doses of 500 mg thrice daily for 7 days, preferably starting within 72 hours of onset of rash.

In one masked controlled study of 454 patients with HZO receiving oral famciclovir (500 mg thrice daily) or oral acyclovir (800 mg 5 times daily) for 7 days, percentages of patients who experienced ocular manifestations were similar for famciclovir (58.0% [142/245]) and acyclovir (58.2% [114/196]) recipients, with no significant difference between groups in both complications and severity, including visual loss.[45] Shafran et al reported that famciclovir (750 mg peroral every day, 500 mg peroral twice daily, or 250 mg peroral thrice daily) was comparable in efficacy to acyclovir (800 mg 5 times daily). Again, PHN was not addressed.[46]

However, clinical studies in several hundred immunocompetent, nonophthalmic zoster patients have noted a clinically and economically worthwhile effect on PHN. Famciclovir (500 mg peroral thrice daily) was compared with a placebo or acyclovir (800 mg 5 times daily) for 7 days. Results were clearly superior to those with a placebo and similar to those with acyclovir both in stopping viral shedding and accelerating dermal healing. Perhaps more importantly, famciclovir had a significantly greater effect on the duration of PHN compared with a placebo. With an incidence of just over 50% in all groups, the median time to resolution of the neuralgia was 55 and 62 days in the famciclovir groups, compared with 128 days in the placebo group.[31] Dworkin et al have also reported that treatment of acute HZ patients with famciclovir significantly reduces both the duration and prevalence of PHN.[47] The overall efficacy has been confirmed by others.[48,49]

Clinical comparison of valacyclovir with famciclovir shows the drugs to be comparable in the treatment of nonocular VZV in terms of cutaneous healing and pain resolution. In one study, 597 immunocompetent patients 50 years and older presenting within 72 hours of onset of zoster rash were treated with valacyclovir (1 g peroral thrice daily) or famciclovir (500 mg peroral thrice daily) for 7 days. Resolution of zoster-associated pain and PHN, rash healing, and treatment safety were comparable between the two groups, as was safety.[31] In brief, all 3 oral antivirals, acyclovir, valacyclovir, and famciclovir, have comparable efficacies in the treatment of HZ and HZO, particularly in terms of resolution of acute pain, rash, viral shedding, and ocular complications such as conjunctivitis, keratitis, iritis, and scleritis. Valacyclovir and famciclovir, however, although they do not reliably prevent PHN, do offer statistical superiority over acyclovir in reducing the incidence, severity, and duration of PHN, one of the most serious zoster complications and one that is more common in patients with HZO.[27] This factor alone puts acyclovir into a secondary position therapeutically and makes valacyclovir and famciclovir the drugs of choice for therapy of HZO and HZ.

Corticosteroids

In the era of oral antivirals, systemic steroids have become less controversial. Immunocompetent patients (N = 208) older than 50 years with HZ received acyclovir (800 mg peroral 5 times daily) or a placebo within 72 hours of rash onset for 21 days.[50] Patients were given prednisone or placebo perorally at 60 mg/day for the first 7 days, 30 mg/day on days 8 to 14, and 15 mg/day on days 15 to 21. Patients receiving prednisone had statistically significant acceleration in the rate of cutaneous healing and relief of acute pain. There was also an improved quality of life: less need for analgesics, more uninterrupted sleep, shorter time to resumption of usual activities, and no adverse drug effect. Other studies produced similar results, but none demonstrated any effect on PHN.[50,51]

Corticosteroids can be considered as soon after diagnosis as possible for patients with at least moderately severe pain not controlled by 3 days of opioids (see below), severe rash, or VZV-induced facial paralysis and cranial polyneuritis to improve motor outcomes. Because of the potential risks of systemic steroids in acute zoster, this treatment should probably be limited to those at minimal risk for adverse steroid reaction (e.g., nonimmunocompromised patients, nondiabetic patients, those without GI ulcers).

Acute Pain and Postherpetic Neuralgia/Itch

Risk Factors, Incidence, and Mechanisms

Although it is clear that early antiviral therapy (within 72 hours after rash onset), particularly with valacyclovir or famciclovir, plays a critical role in controlling acute and long-term HZ pain, other analgesics are also indicated in the vast majority of patients.[48,52] The acute pain experienced by patients during the early phases of HZO is attributed, in part, to inflammatory swelling of the trigeminal nerve (fifth nerve) and to the pain of inflammatory reactions in and around the eye itself and in the CNS.[53] This pain is often lancinating, burning, aching, and/or itching and is accompanied by sympathetic hyperactivity such as tachypnea, tachycardia, diaphoresis, mydriasis, and an effect characterized by anxiety.

Postherpetic neuralgia and postherpetic itch (PHI) are defined most commonly as zoster pain or itch lasting more than 1 month after acute disease onset. Symptomatology is grouped under the term *postherpetic neuralgia* and includes constant or intermittent aching or burning, sudden lancinating pain, allodynia (pain from nonpainful stimuli), and/or a constant or intermittent PHI in the involved area. Risk factors for PHN include older age (>60 years); greater prodromal and acute disease pain; marked rash severity; rash on head, face, or neck (particularly ophthalmic); clinical depression; adverse psychosocial factors; failure to treat with valacyclovir or famciclovir; and viremia.[47,54–58] Mechanical allodynia (touch) and pinprick hypesthesia are strongly associated with the development of PHN and are risk factors for predicting PHN. By contrast, lack of allodynia during the acute stages of HZ predict uneventful recovery by 3 months.[56] Chronic pain, including PHN, is associated with quiescent behavior, which is often overlooked by the treating physician. Such behavior includes sleep disturbance, lassitude, anorexia, weight loss, constipation, and, in place of anxiety, depression.

Postherpetic neuralgia persists in 9.3% to 17% of HZ patients, with the higher incidence and severity in the sixth through eighth decades of life.[3,4] Scott et al found that the prevalence of PHN was 30% at 6 weeks after rash onset, 27% at 12 weeks, 15.9% at 6 months, and 9% at 1 year.[57] Bowsher reported that, of 1071 HZ patients (534 men and 537 women) with a median age of 80 years, 15% of those who had shingles developed PHN. In 17 of 62 patients with PHN, it was ongoing for years.[59] It is notable that the incidence of PHN is higher in HZO than in other forms of zoster.[3,58–60]

Both incidence and duration/severity of PHN increase with age. In a study of 916 HZ patients, 12.5% of those 20 or younger developed acute neuralgia, 40% developed it in the third and fourth decades of life, and only 20% developed it in their sixth and seventh decades.[61] In contrast, within this same population the incidence of chronic PHN lasting more than 1 year fell to <4% among those patients under 20 and 10% in those patients in the third and fourth decades of life, but rose to nearly 50% in those patients in the sixth decade.

Postmortem examination of those who die during acute VZV shows lymphocytic infiltration and necrosis of the ganglia, and viral particles in granulomatous arteritis.[62] Cerebrovascular accidents are not infrequent.[63] Virus particles have also been found in acute VZV in the trigeminal ganglion and its axons, in CNS tissues, and in the arterial walls of ocular and CNS tissues.[64] Years after acute HZO, findings may include chronic granulomatous intracranial arteritis as well as neuronal and myelin loss, chronic inflammation, and glial nodules in the brain stem extending from the pons to the second cervical segment of the medulla in the mesencephalic trigeminal pain nucleus[64–66]; for more than 10 years, findings revealed no CNS morphologic abnormalities but did reveal severe pathologic damage to the ophthalmic and supraorbital nerves, including fibrosis, demyelination, loss of myelinated fibers, and shift in fiber diameter to pain-transmitting small-diameter neurons (nociceptors).

Recurrent ganglionitis may also contribute to PHN. In a case study of an immunocompetent elderly woman with intermittent PHN over 11 years, she had mononuclear cells containing VZV DNA during recurrent pain. The patient was treated with famciclovir 5 times. Each treatment relieved the pain, but pain always recurred within 1 week of stopping the drug; blood mononuclear cells contained the VZV genome, and there was increased cell-mediated immunity to VZV on all 5 occasions.[67,68] Varicella-zoster virus–specific proteins are also found in the monocytes of PHN patients months or years after the acute disease, indicating persistence, reactivation, and expression of VZV.[69]

The pathophysiology of PHN in its many forms, then, is multifactorial and not fully understood. In brief, PHN and PHI appear to be the result of disordered fiber input into a diseased sensory ganglion, damaged spinal pain pathways with ectopic firing to the cerebral cortex, abnormally heightened skin nociceptor sensitivity, and, in some cases, reactivated ganglionitis.[54,56,65,67,68,70–73]

Medical Management of Acute Pain, Postherpetic Neuralgia, and Postherpetic Itch

The importance of understanding and addressing the prevention and management of PHN early cannot be emphasized enough. As Oster et al have noted, older persons (>65 years) with PHN experience longstanding, severe, debilitating pain and poor health-related quality of life.[74] Patient dissatisfaction with treatment is high because many physicians do not make the effort to work out the optimal medication regimen to relieve this very debilitating disease. Prophylactic vaccination with the herpes zoster vaccine is the best method for preventing PHN, but in patients who have already developed a zoster rash, initiating oral valacyclovir or famciclovir as early as possible (preferably within 48–72 hours of rash onset) offers some benefit, as discussed above.[48,52]

Drugs for Postherpetic Neuralgia and Postherpetic Itch

Meta-analysis of analgesic therapy in PHN by Hempenstall et al revealed that there is ample evidence to support the use of the orally administered therapies TCAs, strong opioids, gabapentin, and pregabalin. Topical therapies associated with efficacy were lidocaine 5% ointment, lidocaine–prilocaine cream (EMLA, AstraZeneca LP, Wilmington, DE), or lidocaine patch.[75] To this list, the author adds diphenhydramine (Benadryl, McNeil-PPC, Inc., Morris Plains, NJ) cream and/or pills (25–50 mg peroral at bedtime or in divided doses every 12 hours) as an additional agent for PHI. Periodic drug tapering should be attempted, as PHN may decrease spontaneously over time.

Tricyclic Antidepressants in Postherpetic Neuralgia. Tricyclic antidepressants have been successfully used to treat chronic neuropathic pain of numerous etiologies.[32,76,77] Pain relief is thought to be a result of these drugs' norepinephrine and serotonin reuptake-blocking properties, which increase the inhibition of spinal neurons involved in conscious pain perception, thus relieving or preventing pain.[78]

In a placebo-controlled study, the significant clinical value of the TCA amitriptyline (25–150 mg peroral every day) was noted in elderly patients with permanent PHN.[79,80] In 66% of patients, pain was reduced from severe to mild within 3 weeks. In this study, serum amitriptyline levels were below those associated with antidepressant activity. However, increased dosage produced increased pain in some patients, suggesting a therapeutic window for the analgesic dosage of the TCAs. Analgesia was generally achieved at levels half those required for antidepressant effect and occurred within 2 weeks of initiating treatment.[81]

Nortriptyline has demonstrated efficacy similar to that of amitriptyline in head-to-head trials but has the advantage of being associated with fewer side effects.[80] Combination of either doxepin or amitriptyline with a narcotic analgesic reduced pain intensity more than either a TCA or a narcotic drug alone in patients suffering chronic neuralgic pain. A different TCA may be used as indicated below, depending on side effect profile.[71,75,82,83]

The time at which TCA treatment is begun is a critical factor in determining treatment outcome.[76,84] If started between 3 and 12 months after acute HZ onset, 66% of patients receiving a TCA obtain pain relief; between 13 and 24 months, 41%; and at more than 2 years, 30%. Background and paroxysmal pain disappear earlier and are significantly more responsive to a TCA than allodynia or burning pain; the latter 2 prognosticate unsatisfactory response to TCA therapy ($P<0.0001$). Twice as many patients (86%) with PHN without allodynia obtain pain relief as those with allodynia (42%). Although TCAs are extremely important in treating various forms of PHN, other agents might need to be added to cover unresponsive symptoms such as allodynia and burning.

Because there is little difference in efficacy among the TCAs for treatment of pain, drug selection may depend on the side effects. The tertiary amines amitriptyline, imipramine, and doxepin have more anticholinergic, cardiac, and CNS effects than the demethylated secondary amines nortriptyline and desipramine. Therefore, in the more vegetative patient desipramine may be the least sedating, whereas an agitated patient may benefit more from amitriptyline or doxepin. Nortriptyline is the drug of choice in patients with bradycardia or heart block.[77] Dosage is similar for all agents: 25 to 50 mg peroral every day at bedtime or in divided doses every 12 hours, in increasing increments every 7 days to a stable dose of 25 to 100 mg daily as tolerated.

Anticonvulsants. The anticonvulsant gabapentin (Neurontin, Pfizer Inc., New York, NY; 600 mg peroral 2–6 times daily) is frequently very effective at controlling PHN as a single agent and may be given intermittently or continuously for months to years as tolerated or needed.[85–87] The mechanism of action appears to be multifactorial. Taylor et al report that gabapentin (1) increases the concentration and, probably, the rate of synthesis of γ-aminobutyric acid in the brain, enhancing nonvesicular γ-aminobutyric acid release during seizures; (2) occupies a binding site in brain tissue associated with voltage-sensitive Ca^{2+} channels; (3) may modulate certain types of Ca^{2+} current; (4) reduces release of several monoamine neurotransmitters; (5) inhibits voltage-activated Na^{+} channels; and (6) increases serotonin concentrations in human whole blood relevant to neurobehavioral actions.[88]

The efficacy of gabapentin was reported in a total of 563 HZ patients with PHN persisting for at least 3 months after healing of the rash.[89] Using a maximum target dosage of 3600 mg/day, gabapentin produced significant reductions in mean daily pain scores compared with a placebo, enhanced overall quality of life in patients with chronic PHN, and reduced their need for opioids. It was especially effective against allodynia, a neuralgia not particularly responsive to TCAs. A second double-blind placebo-controlled crossover study found that gabapentin (900 mg) decreased pain severity by 66%, compared with 33% for a placebo, and also achieved greater reductions in allodynia area and severity, and overall pain relief.[90]

In an earlier dose-ranging study, Jean et al studied 32 male and 29 female subjects and found that the intensity of pain greatly lessened in all patients after 3 days of treatment, regardless of whether individuals received 200 mg, 400 mg, or 600 mg of gabapentin. Common adverse events, such as dizziness, drowsiness, or fatigue, also did not differ among the dose groups, suggesting that 600 mg/day is a safe and effective starting dose of gabapentin for patients with PHN.[91] This dose could be gradually raised to as high as 3600 mg/day, as needed. Tapering may be attempted periodically to see if a lower dose will control symptomatology with time.

Pregabalin (Lyrica, Pfizer), classified as a narcotic, has a pharmacologic profile similar to that of its predecessor, gabapentin, but showed greater analgesic activity in rodent models of neuropathic pain. The mechanism of action is unclear, although it may reduce excitatory neurotransmitter release by blocking voltage-gated calcium channels. Oral pregabalin, 300 to 600 mg/day (600 mg maximum/day), was significantly superior to a placebo in relieving pain and improving sleep in double-blind placebo-controlled studies in a total of 776 patients with PHN. In 2 studies, significant improvements in mean daily pain scores were apparent on the first or second day of treatment with pregabalin thrice daily, which is somewhat earlier than when relief occurs with gabapentin. The drug was generally well tolerated (to a maximum of 600 mg/day) in clinical trials that enrolled mostly elderly PHN patients,[92,93] although the author has seen patients with severe somnolence on 50 mg/day (unpublished data). Dizziness, somnolence, and peripheral edema are the most common adverse events.[92–94]

Both gabapentin and pregabalin are FDA approved for treatment of PHN.

Combination Therapy and Opioids. For patients not responding satisfactorily to single-agent therapy, gabapentin and a TCA such as nortriptyline or desipramine may be combined for additive effect.[95] If the combination is still not totally effective or if one or both drugs are not tolerated in treatment of PHN, slow-release opioids such as oxycodone hydrochloride controlled-release (OxyContin, Purdue Pharma L.P., Stamford, CT; 10–30 mg peroral every 12 hours) may be added or given as a single agent to provide additional relief without a high and with little chance of

addiction. Controlled-release oxycodone is effective for relief of steady or paroxysmal pain and allodynia.[85,96,97]

Topical Analgesics. Topical lidocaine is often very effective for allodynia and itch as well as ache and lancinating pain and may be added to any or all of the above pain agents.[98–101] The mechanism of action is by blocking the voltage-gated Na^+ channels on excitable membranes, thereby preventing the generation and conduction of nerve impulses.[99] There is some evidence to suggest that lidocaine may offer greater benefit to those with impaired nociceptor function as a result of PHN: Wasner et al found that these patients and those with no or few remaining nociceptors experienced significant pain relief, whereas those with preserved or sensitized nociceptors experienced no benefit relative to a placebo. Their findings also supported the hypothesis that at least some PHN pain arises from sensitized nociceptors.[102]

Forms of lidocaine that are most useful for HZO are lidocaine 5% ointment or lidocaine–prilocaine cream, which may be applied every 4 to 6 hours as needed. The 5% lidocaine patch is also effective but sometimes difficult to apply on the face or in the hair.[96,98]

Capsaicin cream depletes the pain neurotransmitter substance P from the small sensory peripheral neurons. It is prescribed by some physicians but is generally poorly tolerated because of burning, stinging, or erythema in 30% of patients.[103] It has largely fallen out of use with the availability of the lidocaine agents.[75,96,104,105]

Other Forms of Acute Pain and Postherpetic Neuralgia Control. Nerve blocks of the supraorbital, infraorbital, and supranasal nerves with bupivacaine or methylprednisolone may be given for severe acute HZO pain, with notable efficacy.[106–108] Botulinum map injections are effective in 50% of patients with intractable HZO PHN (Borodic G, personal communication, 2006).[99,109,110]

Conclusion

If started within 72 hours of onset of the acute HZ rash, the oral antiviral agents acyclovir, valacyclovir, and famciclovir significantly shorten the periods of acute pain, virus shedding, rash, acute and late onset anterior segment complications, and, in the case of valacyclovir and famciclovir, the incidence and severity of PHN. However, these medications do not prevent PHN, which remains a common and debilitating complication of HZ in older patients that requires assiduous pain management. Tricyclic antidepressants, antiseizure drugs, opioids, and topical analgesics all offer some pain relief and may be combined. Prevention of HZ and its complications via vaccination remains the best course for reducing zoster-associated morbidity and mortality; however, in patients who have already developed HZ aggressive managing can alleviate both the acute phase and the pain of PHN.

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