Clinical trial

A retrospective study on the clinical outcome of herpes zoster in patients treated with acyclovir or valaciclovir vs. patients not treated with antiviral

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Two hundred and forty-four patients with herpes zoster were reviewed. One hundred and sixty-four did not receive antiviral therapy, 29 received acyclovir, and 51 received valaciclovir. These three groups of patients were comparable by age and sex distribution. The time for a scab to form was significantly shorter for patients receiving acyclovir (mean of 8 days) and valaciclovir (mean of 6.8 days) than those who did not receive antivirals (mean of 11 days). The time taken for skin lesions to heal completely was significantly shorter for patients receiving acyclovir (mean of 16 days) and valaciclovir (mean of 13 days) than those who did not receive antivirals (mean of 21 days). The proportion of patients with post-herpetic neuralgia decrease over time in all three groups. The proportions of patients with post-herpetic neuralgia who did not receive antivirals were 49%, 27%, 18%, and 16% at 1, 3, 6, and over 6 months respectively. The corresponding proportions for patients receiving acyclovir were 48%, 24%, 17%, and 14% and, for valaciclovir, were 23%, 6%, 0%, and 6%.

Clinical assessment

All patients with herpes zoster seen at a dermatology referral center between January 1994 and December 1995 were included in the study. Patients' demographic data, prodromal symptoms, clinical presentation, location of zosters, time taken for scabbing (presence of dried crusts on erosions) and complete healing (disappearance of scab and complete re-epithelialization of erosions), and post-herpetic neuralgia at 1, 3, 6, and over 6 months after the appearance of skin eruptions were obtained from the case records. The severity of pain, itching, and paresthesia was recorded using a visual analog scale with 0 = no symptom and 10 = extreme/intolerable symptom. Patients were contacted by telephone to obtain any missing information required in the study.

The study compared the clinical outcome of patients who received antiviral treatment with those who did not. The standard regimen for the treatment of herpes zoster in the National Skin Centre consists of oral acyclovir 800 mg, five times per day for 7 days, or valaciclovir 1 g, three times per day for 7 days (and later famciclovir 250 mg, three times per day for 7 days). The choice of antivirals is based on the discretion of the dermatologists managing the patients. The standard guidelines for prescribing the antivirals include early zoster lesions (within 72 h of appearance of blisters) and severe progressing lesions and zosters on the face. Patients who did not receive antiviral treatment represented those who presented more than 3 days after the appearance of their skin eruption or those who did not want antiviral treatment (mostly because of cost).

The chi-squared test and Levene's test for equality of variance were used to compare the statistical significance; p values of less than 0.05 were considered to be significant.

Results

Table 1 shows the demographic data of the study cohort. The mean age, age group distribution, and sex distribution were similar in all three groups of patients. Fifty-nine per cent of patients experienced prodromal pain, 23.4% experienced itching, and 16% experienced paresthesia. With the onset of the eruption, 96.7% experienced pain, 17.2% felt stressed, 16.4% experienced tiredness, 11.9% had flu-like symptoms, and 5.7% felt depressed. The pain was commonly described as burning (31.3%), stabbing (14.8%), shooting (15.2%), and aching (11.3%). The proportions of patients with various prodromal and acute symptoms were not statistically different among the three groups.

Table 1 Profiles of herpes zoster patients: no treatment vs. acyclovir vs. valaciclovir

	No treatment (n = 164)	Acyclovir (n = 29)	Valaciclovir (n = 51)	Total (n = 244)
Age (mean) in years	48.7 (SD 17.9)	47 (SD 14.1)	48.7 (SD 20.4)	48.9 (SD 18)
Men	84 (51.2%)	14 (48.3%)	28 (54.9%)	126 (51.6%)
Women	80 (48.8%)	15 (51.7%)	23 (45.1%)	118 (48.4%)
Age of onset				
<30 years	23 (17.1%)	4 (13.8%)	8 (15.7%)	40 (16.4%)
30–50 years	67 (40.9%)	14 (48.3%)	22 (43.1%))	103 (42.2%)
>50 years	69 (42.0%)	11 (37.9%)	21 (42.2%)	101 (41.4%)

Table 2 Duration of lesional skin healing in herpes zoster: no treatment vs. acyclovir vs. valaciclovir

	No treatment (n = 164)	Acyclovir (n = 29)	Valaciclovir (n = 51)
Scabbing	11.1 days (SD 4.4)	8.2 days (SD 2.4) (p = 0.005)	6.8 days (SD 1.8) (p = 0.001)
Complete skin healing	20.8 days (SD 9.5)	16.4 days (SD 6.3) (ns)	13.4 days (SD 13) (p = 0.007)

Table 3 Post-herpetic neuralgia at 1, 3, 6, and over 6 months: no treatment vs. acyclovir vs. valaciclovir

	No treatment (n = 164)	Acyclovir (n = 29)	Valaciclovir (n = 51)
1 month			
Pain present	81 (49.4%)	14 (48.3%) (ns)	12 (23.5%) (p < 0.002)
Severity	2.2 (SD 1.7)	1.6 (SD 0.8) (ns)	1.3 (SD 1.2) (ns)
3 months			
Pain present	45 (27.4%)	7 (24.1%) (ns)	3 (5.9%) (p < 0.002)
Severity	2.0 (SD 1.6)	1.1 (SD 0.4) (ns)	1.0 (SD 0.0) (ns)
6 months			
Pain present	29 (17.7%)	5 (17.2%) (ns)	0 (0%) (p < 0.002)
Severity	1.9 (SD 1.7)	1.0 (SD 0.0) (ns)	0 (ns)
>6 months			
Pain present	26 (15.9%)	4 (13.8%) (ns)	3 (5.9%) (ns)
Severity	1.7 (SD 1.5)	1.0 (SD 0.0) (ns)	1.0 (SD 0.0) (ns)

Table 2 shows the time taken for the blisters to dry up and for the skin lesion to heal completely among the three groups of patients. The duration of complete healing was longest in the untreated group, followed by those treated with acyclovir ($p < 0.005$) and those treated with valaciclovir ($p < 0.001$).

Table 3 shows the proportions of patients with post-herpetic neuralgia at 1, 3, 6, and over 6 months after the appearance of the skin eruptions. The proportion of patients with post-herpetic neuralgia decreased over time in all three groups; however, the proportion of patients with persistent pain was significantly higher in the untreated group than in those treated with acyclovir and valaciclovir ($p < 0.001$ at 1, 3, and 6 months). Three patients who received valaciclovir experienced recurrence of pain after being pain free at 6 months.

Discussion

The risk of herpes zoster appears to increase with age. The annual incidence of herpes zoster ranges from 0.4 to 1.6 cases per 1000 among healthy people under 20 years of age to 4.5 to 11 cases per 1000 among those over 80 years of age.[1–7] The mean age of our patients was 49 years. Herpes zoster was certainly not uncommon in the young in our study as 17% of our patients were less than 30 years of age.

Pain is usually the most uncomfortable sensation associated with herpes zoster.[3,8–10] Any medication which can reduce the severity and duration of acute and chronic pain of herpes zoster will benefit patients. Acute zoster pain generally refers to the initial acute pain prior to, during, or within 4 weeks of zoster skin eruption. Post-herpetic neuralgia generally refers to pain persisting 4–6 weeks after the appearance of the skin eruption. About half of our patients experienced pain as a prodromal symptom and almost all patients experienced pain with the onset of skin eruptions. Pain is generally more severe during the onset of skin eruptions than during the prodromal period. Older patients (over 50 years, 42%) are more likely to experience prodromal pain than younger patients (less than 30 years, 25%).

Several studies appear to indicate that early treatment of herpes zoster with antiviral agents may reduce the severity of acute pain and decrease the prevalence of post-herpetic neuralgia.[8,11–16] Our study showed that the time for scabs to form was significantly shorter for patients receiving acyclovir (mean of 8 days) and valaciclovir (mean

of 6.8 days) than those who did not receive any antiviral (mean of 11 days). The time taken for complete healing was also significantly shorter for patients who were treated with acyclovir (mean of 16 days) and valaciclovir (mean of 13 days) compared with those who did not receive antiviral treatment (mean of 21 days). Post-herpetic neuralgia was more common among the older patients (over 50 years) in all three study groups. For the older patients (over 50 years) who did not receive antiviral treatment, the proportions of patients with post-herpetic neuralgia at 1, 3, 6, and over 6 months were 62%, 39%, 23%, and 20%. The corresponding values for patients less than 30 years of age were 29%, 11%, 7%, and 7%. The proportion of patients with post-herpetic neuralgia decreased over time in all three groups. Our findings indicated that patients receiving acyclovir appeared to have a lower risk of developing post-herpetic neuralgia at 1, 3, and 6 months compared with those who did not receive antiviral treatment, but the difference was not statistically significant. In contrast, patients who received valaciclovir experienced a significantly lower prevalence of post-herpetic neuralgia compared with those who were treated with acyclovir and those who did not receive antiviral treatment ($p < 0.001$). The proportions of patients who experienced post-herpetic neuralgia at 1, 3, and 6 months for untreated individuals was 48.4%, 27.4%, and 17.7%, compared with 23.5%, 5.9%, and 0% for the valaciclovir group and 15.9%, 13.6%, and 5.9% for the acyclovir group. Three of our patients who received valaciclovir treatment experienced pain again after more than 6 months although they were pain free at 6 months. Valaciclovir, the L-valyl ester of acyclovir, is rapidly converted to acyclovir after oral administration, and results in an acyclovir bioavailability three to five times greater than that of oral acyclovir in humans.[17,18] The achievement of higher concentrations than those attained with the standard oral acyclovir regimen could result in improved benefit, particularly for post-herpetic neuralgia, with valaciclovir.[19] Our study appears to support this observation. Valaciclovir appeared to be more effective than acyclovir in reducing morbidity from herpes zoster.

Our study also indicated that the greatest impact of pain (acute and chronic) on patients with herpes zoster was insomnia. It occurred among all patients, regardless of whether they were treated with antivirals. This impact was also most frequently seen in older patients. Therefore, hypnotics or tranquilizers should be prescribed whenever indicated.

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