

Clinical efficacy and tolerability of valacyclovir versus acyclovir in treatment of herpes zoster

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Conflict of interest: None to declare

Received: April 7, 2011
 Accepted: May 24, 2011

Background: Acyclovir, a specific and selective inhibitor of replication of herpesviridae family, has well documented efficacy for speedy rash healing and decreasing pain of herpes zoster. Limited oral bioavailability of acyclovir requires frequent dosing. Valacyclovir is rapidly and almost completely converted to acyclovir in vivo and gives three to fivefold increase in acyclovir bioavailability. The aim of this study was to assess the clinical efficacy, safety and tolerability of oral valacyclovir versus standard oral acyclovir in the treatment of herpes zoster.

Methods: A blind randomized prospective study was performed during May 2007 to August 2007 in Midnapore Medical College. Immunocompetent patients, aged ≥ 40 yrs presenting with herpes zoster within 72 hours after onset of rash were enrolled and randomized to receive one of the following treatments: 1000 mg of valacyclovir thrice daily for 7 days or acyclovir 800 mg 5 times daily for 7 days. A total of 60 patients were included and randomized to receive either valacyclovir (n=30) or acyclovir (n=30) and they were evaluated at 8 days, 15 days and 29 days, respectively.

Results: A statistically significant reduction of skin lesion and zoster associated pain were noticed in valacyclovir compared to acyclovir group. However, presence of post herpetic neuralgia on the 29th day was less in acyclovir compared to valacyclovir group (70.0% vs. 83.3%, $P>0.05$). Only one patient on valacyclovir and two patients on acyclovir complained of nausea and mild abdominal pain.

Conclusion: We conclude that for the management of herpes zoster, valacyclovir might be superior to acyclovir in respect to reduction of skin lesions and pain.

Keywords: acyclovir, herpes zoster, treatment, valacyclovir

Iran J Dermatol 2011; 14: 52-57

INTRODUCTION

Herpes zoster remains an important medical problem throughout the world. It may occur at any age in the otherwise immunocompetent individuals. The reported incidence in the general population ranges from 0.8 to 4.8 per 1000 persons¹. The characteristic rash and associated pain may occur

when varicella zoster, which becomes dormant in sensory ganglia following primary varicella zoster virus infection, is reactivated, often in association with declining cellular immunity associated with advancing age². Post herpetic neuralgia is one of the most common complications of herpes zoster. The incidence of post herpetic neuralgia varies with age. It is rare under 40 years but about 50%

of patients over 60 years may be affected ³.

Acute herpes zoster presents with skin rashes distributed over one or more dermatomes that usually resolve within 4 weeks; however, in an untreated patient, the associated pain and post herpetic neuralgia, may persist for several months to even years and can be a serious disabling condition, particularly in the elderly ^{4,6}. Replication of varicella zoster virus in the ganglion of involved nerve results in destructive inflammation and / or nerve dysfunction. This may partly explain the pain, although the full pathogenesis of the syndrome is not clear ⁶.

Oral Acyclovir (800mg five times daily) is widely used for the treatment of acute herpes zoster. It speeds rash healing and decreases the severity of acute pain ^{7,8}. In some studies, acyclovir also appears to reduce the prevalence, severity and duration of chronic pain ^{6,9}. The limited oral bioavailability of acyclovir, however, necessitates frequent dosing to achieve a better therapeutic concentration in plasma for the treatment of acute herpes zoster ^{4,7}.

Valacyclovir, 2-[2-amino-1, 6-dihydro-6-oxo-9H-purin-9-yl-methoxy] ethyl valinate hydrochloride, is the L-valine ester of acyclovir. It was developed to provide increased oral bioavailability of acyclovir ¹⁰. Valacyclovir is better absorbed than acyclovir due to an active stereoselective transporter in intestinal brush border membrane. Valacyclovir is converted rapidly and virtually to acyclovir after oral administration in healthy adults by intestinal and hepatic first pass metabolism through hydrolysis. Thus, the mechanism of action and spectrum of activity of valacyclovir are the same as that of acyclovir. Unlike acyclovir, valacyclovir is a substrate for intestinal and renal peptide transporters. Therefore, the proportion of bioavailability of acyclovir increases 3-5 times greater to approximately 70% following valacyclovir administration ¹¹. The comparatively better oral bioavailability of valacyclovir contributes to the need for less frequent administration. Apart from the differences in bioavailability, the mechanism, clinical spectrum and adverse effects are similar ¹².

This randomized prospective study was conducted in Midnapore Medical College and Hospital to assess the clinical efficacy, safety and tolerability of oral valacyclovir versus standard oral acyclovir in the treatment of herpes zoster.

PATIENTS AND METHODS

This randomized prospective study of valacyclovir versus acyclovir for the treatment of acute herpes zoster was carried out in Midnapore Medical College and Hospital between March 2007 and August 2007.

Patients

Non-pregnant patients who were 40 years of age or older, were immunocompetent and were not on any immunosuppressive medication and presented within 72 hours after the onset of rash were enrolled in the study. The clinical diagnosis of herpes zoster was based on the presence of unilateral dermatomal rash. The ethics committee of Midnapore Medical College and Hospital approved the study protocol. A written informed consent was obtained from each patient prior to enrollment. Routine hematological examination, liver function test and renal function test (urea and creatinine) were done before the treatment and after completion of valacyclovir / acyclovir therapy.

Drug administration

A total of sixty patients were included in the study. Out of them, 30 patients were treated with valacyclovir and remaining 30 patients with acyclovir. The patients were selected randomly, those with even number were put on valacyclovir and the odd ones were given acyclovir. Thus, the patients were randomized to receive either 1000 mg valacyclovir three times daily from the day of presentation for 7 days or oral acyclovir 800 mg five times daily for the same period.

Efficacy assessment

At the time of presentation, the patients were evaluated for zoster rashes including the proportion of the total lesion area consisting of macules/papules, vesicles, crusts and healed rashes, the distribution of rash (trigeminal, cervical, thoracic and lumbosacral) and prodromal symptoms. The patients were reviewed after 1 week (8th day), 2 weeks (15th day) and 4 weeks (29th day) to assess response to treatment in both groups. The responses were evaluated by the percentage of improvement

in skin lesion and zoster associated pain in each visit and the appearance of post herpetic neuralgia after the 4th week.

The impact of pain on daily activities was determined using a numerical scale with six levels as follows ¹³.

No Pain	0 = no pain and discomfort
Just noticeable	1 = Pain can easily be ignored
Mild	2 = Pain does not interfere with daily activities
Moderate	3 = pain interfered with concentration or sleep
Severe	4 = Pain interfered with all but basic needs
Very Severe	5 = Pain required rest or bed rest

All adverse effects were recorded during the follow-up period.

Statistical analysis

Student t-test, odds ratio (OR) and 95% confidence interval (CI) was calculated following standard statistical method. The differences in the severity of zoster associated pain, skin rash and presence of post herpetic neuralgia between the two treatment groups was compared using chi-square test. All statistical tests were done using EPI6 statistical package. A p-value less than 0.05 was considered significant.

RESULT

A total of 60 patients with herpes zoster were enrolled in the study. They were randomized into two groups- valacyclovir (n = 30) and acyclovir (n = 30). All the patients completed the 4-week study period and were reviewed after one week,

two weeks and four weeks. None of these patients withdrew because of serious adverse events. Only one patient on valacyclovir and two patients on acyclovir complained of nausea and mild abdominal pain, but they continued the treatment. More importantly, no abnormalities were detected during the routine hematological, liver or renal function tests either before or after treatment.

Of 60 patients, 40 (66.7%) were male and 20 (33.3%) were female. The mean age of the patients was 51.9 ± 8.9 years; no significant difference was observed between two treatment groups. Moreover, there were no significant differences between two groups in other basic characteristics. There were four types of herpes zoster patients in this study; among them thoracic type is the commonest (56.6%). Other types are cervical (28.3%), trigeminal (10%) and lumbosacral (5%). Most of the patients (60.0%) complained of prodromal symptoms (Table 1).

During the 1st review period (i.e. the 8th day), we noticed that most of the patients improved partially. We accepted the 75% skin lesion improvement as the significant improvement on the 8th day of treatment. By the 15th day, most of the patients showed complete healing of the skin lesions. Hence, on the 15th day, we accepted 100% improvement as the significant improvement (Figure 1,2).

The changes in skin lesions following the treatment are presented in Table 2. Faster resolution of skin lesions was noted in the valacyclovir group compared to acyclovir group during the 1st review (the 8th day) (90.0% vs. 20.0%) and the 2nd review (15th day) (93.3% vs. 30%) and the comparison was statistically significant ($p < 0.001$). After the 4th week, skin lesions healed completely in all the patients of both groups.

Table 3 presents the rate of zoster-associated pain after treatment. At 8th day, zoster associated

Table 1. Demographic characteristics of patients

Characteristics of patients	Total patients	Acyclovir	Valacyclovir	p-value
Age (year) Mean \pm SD	51.9 \pm 8.9	50.7 \pm 8.7	53.2 \pm 8.9	0.276
Sex				
Male	40 (66.6%)	19 (63.3%)	21 (70.0%)	0.782
Female	20 (33.4%)	11 (36.7%)	9 (30.0%)	0.782
Type				
Thoracic	34 (56.6%)	17 (56.7%)	17 (56.7%)	0.794
Cervical	17 (28.3%)	9 (30%)	8 (26.7%)	0.998
Trigeminal	6 (10.0%)	2 (6.7%)	4 (13.3%)	0.673
Lumbosacral	3 (5.0%)	2 (6.7%)	1 (3.3%)	0.991
Presence of Prodromal symptom	36 (60.0%)	19 (63.3%)	17 (56.7%)	0.796



Figure 1. (a) Herpes zoster lesion before treatment with acyclovir. **(b)** Clinical improvement after 7 days of treatment with acyclovir.



Figure 2. (a) Herpes zoster lesion before treatment with valacyclovir. **(b)** Clinical improvement after 7 days of treatment with valacyclovir.

pain was less in the valacyclovir group compared to the acyclovir group (56.7% vs. 36.7%) but the differences was not statistically significant. However, at 15th day, 83.3% of the patients in the valacyclovir group reported no pain compared to 40.0% of patients in the acyclovir group, and the differences was highly significant ($P < 0.001$). Table 4 shows the incidence of post herpetic neuralgia in

both treatment groups as evaluated after 28 days. It was observed that the presence of post herpetic neuralgia was more common in the valacyclovir group than the acyclovir group but with no significant difference (83.3 % vs 70.0%, $p > 0.05$).

Table 2. Comparison of skin changes of herpes zoster in patients treated with acyclovir versus valacyclovir

Days	In Acyclovir Group (n =30)	In Valacyclovir Group (n =30)	p-value
8 th day (75% reduction)	6 (20.0%)	27 (90.0%)	<0.001
15 th Day (100% reduction)	9 (30.0%)	28 (93.3%)	<0.001

DISCUSSION

The 4-week randomized parallel and controlled study demonstrated that treatment with valacyclovir three times daily was effective in treating patients with herpes zoster. Overall, women may have a slightly greater risk of developing zoster when compared to men; but in the present study, we observed that men were more frequently affected than women (66.6% vs. 33.4%)¹⁵. This study showed that the commonest type of herpes zoster

Table 3. Comparative efficacy in improving zoster associated pain.

Days	In Acyclovir Group (n =30)	In Valacyclovir Group (n =30)	p-value
8 th day (75% improvement)	11 (36.7%)	17 (56.7%)	0.196
15 th Day (No pain)	12 (40.0%)	25 (83.3%)	<0.001

Table 4. Incidence of post herpetic neuralgia.

Days	In Acyclovir Group (n =30)	In Valacyclovir Group (n =30)	p-value
29 th day	21 (70.0%)	25 (83.3%)	0.222

was thoracic (56.6%) as mentioned in previous studies¹⁵. The prodromal symptoms commonly preceded the herpes zoster eruption (60%) similar to other studies¹³.

Skin lesions improved faster in patients on valacyclovir compared to acyclovir (93.3% vs. 30.0%) and the difference was statistically significant. An earlier study also noticed the faster resolution of skin lesion in valacyclovir group but their findings were not statistically significant⁴. Pain is the most common debilitating feature of herpes zoster¹³. The majority of the patients experience pain immediately before and during the acute rash phase. However, a more important clinical concern is to prevent or reduce the possibility of persistent pain. A significant improvement in zoster - associated pain was noticed in the present study in patients on valacyclovir compared to acyclovir (83.3% vs. 40.0%) unlike other studies^{4,13}.

Post herpetic neuralgia was more frequently seen in patients who were on valacyclovir rather than acyclovir (83.3% vs. 70.0%) but the difference was not statistically significant. However, a large multicentre study found that the treatment with valacyclovir for 7 days significantly reduced the incidence of the post herpetic neuralgia compared to acyclovir⁴.

A recent review documented that valacyclovir significantly decreased the incidence and severity of post herpetic neuralgia. Valacyclovir recipients had a mean duration of 40 days of pain after lesion resolution compared to 60 days of pain after lesion resolution for acyclovir recipients. In terms of zoster related discomfort, it is estimated that valacyclovir provides a 25% benefit over acyclovir¹². In our study, we also found that skin lesions and zoster associated pain improved significantly faster in the valacyclovir group while we noted no significant reduction in post herpetic neuralgia. The less

frequent dosing schedule of valacyclovir is mainly due to its enhanced bioavailability of 65% compared to 15% to 20% for acyclovir which allows for more convenient dosing adjustment^{7,16,17}.

Safety profile of acyclovir has been carefully established during more than 18 years of clinical use. In the present study, there was no clinically significant difference in nature, frequency or severity of adverse events between the two treatment groups, as reported in earlier studies^{4,13}.

In conclusion, our study demonstrated that administration of valacyclovir three times daily was an effective and safe treatment for acute herpes zoster. Treatment with valacyclovir has the benefits of rapid resolution of skin lesions and zoster associated pain compared to acyclovir, but no additional benefit was noted in the incidence of post herpetic neuralgia. Valacyclovir has the convenience of a three times daily dosing, thereby ensuring better patient compliance, which makes this regimen an excellent choice for treatment of herpes zoster. However, studies on larger numbers of patients are required to assess the incidence of post herpetic neuralgia in treatment with valacyclovir and acyclovir and elucidate the cost effectiveness of valacyclovir versus acyclovir in different societies.

Acknowledgement

The authors gratefully acknowledge the patients for their co-operation during the study period. The authors are also thankful to the authority of Midnapore Medical College & Hospital for logistics support.

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