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Clinical Research

EFFICACY AND SAFETY OF TABLET FAMCICLOVIR 500 MG (PENVIR) IN THE TREATMENT OF OCULAR HERPES

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ABSTRACT

Objective: To assess the efficacy and safety of oral tablet famciclovir 500mg in the management of Ocular Herpes.

Patients and Methods: Patients diagnosed with ocular herpes were enrolled as per inclusion and exclusion criteria. Ophthalmic clinical manifestations, severe and non severe ocular manifestations were recorded at baseline and at day 3 and day 7. Study medication tab famciclovir 500mg was issued to the patients and advised to take orally, one tablet three times a day for 7 days. Safety evaluation was done on day 3 and day 7.

Results: Ophthalmic clinical manifestations, forehead rash, eyelid oedema, photophobia and conjunctival episcleral and circumcorneal conjunctival hyperaemia were statistically significantly reduced on day 3 and day 7. ($p<0.05$, $p<0.01$, $p<0.001$). Statistically significant reduction in ocular pain was seen on day 7 ($p<0.01$). Severe ocular manifestations, deep keratitis resolved completely on day 7, keratic precipitates and synechia resolved on day 3. Non-severe ocular manifestations, episcleritis resolved on day 7. Adverse drug reactions reported were nausea, headache, gastrointestinal intolerance, itching and abdominal cramps, which were of mild to moderate intensity, resolved completely in all the patients. Clinical outcome, analyzed as the cure and improvement taken as success, the treatment was successful in all the patients treated.

Conclusion: In this present study, tablet famciclovir 500mg three times a day for 7 days, was found to be effective in decreasing the symptoms of Ocular herpes and preventing the ocular complications. The study medication was well tolerated.

KEYWORDS : Conjunctivitis, Ocular Herpes, Herpes simplex, Herpes zoster, Famciclovir

Introduction

Ocular Herpes is a challenge for both the clinician and the patient. The major herpes viruses that cause ocular disease - Herpes simplex and Herpes zoster. Herpes simplex in its epithelial form dendritic keratitis is the most common presentation and confusion of these lesions with pseudodendrites a common problem, that can best be solved by remembering two key features of the classic dendritic lesion. True dendritic lesions show arborisation and terminal end bulbs and the possibilities of prior herpes infection if there exists unexplained corneal scarring, corneal hypothesia or iris atrophy. Pseudodendrites can be caused by contact lenses and their solutions, trauma, dry eye, other infections, especially herpes zoster. A good history can be a key tool in differentiating such lesions[1].

Herpes zoster ophthalmicus leads to ocular manifestations ranging from self-limited processes to chronic ocular inflammation or neuropathy, which may lead to serious sequelae like chronic ocular inflammation, vision loss, and disabling pain. Varicella zoster ophthalmicus can be associated with other forms of intraocular disease including iritis, segmental iris atrophy and secondary glaucoma[2].

Current licensure allows to prescribe full range of anti-herpetic agents. Possible manifestations of disseminated herpes outweigh the risk of a suppressed immune response.

Aciclovir has been the mainstay herpetic treatment for years, we tend to prefer the newer prodrug Famciclovir which is converted to Penciclovir upon ingestion and is similarly phosphorylated within infected cells[2].

Oral antivirals are recommended at a dose of 800 mg five times daily for 7 days for Aciclovir, 1000 mg every 8 hours for 7 days for Valacyclovir or 500 mg three times daily for 7 days for Famciclovir.

Famciclovir is the diacetyl 6-deoxy analogue of Penciclovir with same antiviral spectrum as Aciclovir for herpes viruses and has similar potency and selectivity. The oral bioavailability of Penciclovir is 77 % following administration of Famciclovir, significantly higher than the bioavailability of Aciclovir (10-20 %) . The intra cellular half-life of Penciclovir triphosphate is significantly longer than that of Aciclovir triphosphate in cells infected with Varicella zoster virus in vitro (1-11 hours for Penciclovir triphosphate compared with < 1 hour for Aciclovir triphosphate)[2,7].

Famciclovir is approved for treatment of acute uncomplicated herpes zoster. Three doses of Famciclovir 250 mg, 500 mg and 750 mg three times daily are as effective as Aciclovir 800 mg five times daily in cutaneous lesion resolution[2].

Famciclovir's unique pharmacokinetic properties and demonstrated efficacy in acute uncomplicated herpes zoster and probably in Herpes simplex prompted the present investigation of Famciclovir for the treatment of patients with ocular herpes[3].

Rationale of the Study

Famciclovir's unique pharmacokinetic properties and demonstrated efficacy in acute uncomplicated herpes zoster as well as in Herpes simplex prompted the present investigation of Famciclovir for the treatment of patients with ocular herpes.

Hence, the present study is undertaken to evaluate the efficacy and safety of tab Famciclovir 500 mg three times daily for 7 days in the treatment of Ocular herpes.

Patients and Methods:

All the patients attending the outpatient departments and diagnosed clinically to have Ocular Herpes (H.simplex or H.zoster) were enrolled in the present study. Patients aged more than 18 years of age, of either sex, with ocular herpes and requiring medical management or those who were willing to give informed consent, agreeing to come for regular follow up and complying with protocol procedures were included.

Patients excluded were Pregnant and lactating women; Patients received antiviral therapy during previous 14 days, immunocompromised patients, patients on immunomodulatory therapy of any kind and patients known or suspected to be HIV sero - positive.

Written informed consent was obtained from all patients. At baseline visit demographic data, medical history, clinical examination was done and recorded in the CRF. Ophthalmic clinical manifestations like forehead rash, ocular pain, eyelid edema, corneal edema, photophobia, conjunctival episcleral and circumcorneal conjunctival hyperaemia were scored from 1 to 4 depending on the severity, were recorded. Common ocular manifestations of ocular herpes (severe ocular manifestations) like choroiditis, deep keratitis, exophthalmos, optic neuritis, keratic precipitates, scleritis, necrotizing scleritis, synechia, glaucoma and non-severe ocular manifestations like inflammation of conjunctiva, episcleritis, punctate epithelial keratopathy were recorded categorically as Yes/No.

Study medication was issued and the patients were advised to take the study medication tab Famciclovir 500 mg, one tablet three times daily orally for a period of 7 days. Follow up evaluation was done on day 3 and day 7 (end of the study) of therapy. Subjects were monitored for the development of any adverse events and safety evaluation was also done on day 3 and day 7.

Drug supplies: Study medication Tab Famciclovir 500 mg was provided by Hetero Healthcare Limited, Hyderabad.

Concomitant Therapy: Any medication, which was considered necessary for the patient, was used at the discretion of investigator provided it did not interfere with study drug evaluation.

Test for Compliance At follow up visits, patients were asked to bring back the remaining tablets left with them. Compliance was noted by pill count method.

Efficacy Evaluation: Patients were considered clinically evaluable if they have met all pre – therapy and on – therapy criteria and have received study drug. Improvement in ophthalmic clinical manifestations and severe and non severe ocular manifestations at the end of study as compared to baseline. Other variables like patient and as well as Doctor's global evaluation were also analyzed. Clinical outcome at the end of 7 days was also analyzed as cure and improvement were taken as success to the treatment.

Safety Variables: Development of any adverse reactions during the study period were recorded and tabulated.

Statistical Analysis: Standard summary statistics (arithmetic mean and standard deviation) were calculated for all quantitative variables. Categorical variables are presented in frequency tables. Efficacy analyses was based on the full analysis of data set including all patients who received study medication at least once and having at least one measurement of any of the efficacy parameter during the entire treatment period. Safety variables were evaluated for the safety population which include all patients randomized to treatment and who took study medication at least once. Adverse events are summarized by means of appropriate frequency tables.

Results:

Total 43 patients were enrolled into the study. Out of 43 patients, demographic data is available for 30 patients. Out of 30 patients 19 were males and 11 were females, the mean age in years was 45.13 ± 14.63, mean weight in kgs was 60.04±14.22 and mean height in cms was 162.43±9.41 (Table – 1).

Table 1 Patient demographic data

Famciclovir group		
Number of patients (n)	30	
Sex M:F	19:11	
Age (yrs)	Min	18
	Max	71
	Mean	45.13
	± S.D	14.63
Height (cm)	Min	148
	Max	182
	Mean	162.43
	± S.D	9.41
Weight (kg)	Min	39
	Max	90
	Mean	60.04
	± S.D	14.22

Ophthalmic clinical manifestations were recorded in 7 patients. Forehead rash at baseline was 3.42±0.78 and at the end of 3 days it was 2.57±0.53 and at the end of 7 days, it was 1.7±0.75 which was statistically significant reduction ($p<0.05$; $p<0.001$) respectively. There was significant improvement in ocular pain at the end of 7 days as compared to baseline (baseline 3.0±1.0 &7th day1.42±0.53) ($p<0.01$). Eyelid oedema also showed statistically significant improvement at the end of both 3rd and 7th day as compared to baseline. (baseline 3.28±0.95; day three 2.28±0.48 and day seven 1.85±0.9) ($p<0.05$; $p<0.01$) respectively. Similarly, there was statistically significant improvement in photophobia and conjunctival episcleral and circumcorneal conjunctival hyperaemia at day 3 and 7 as compared to baseline ($p<0.05$). However, there was no significant difference in corneal edema at day 3 and day 7 as compared to baseline. (Fig 1, Table 2)

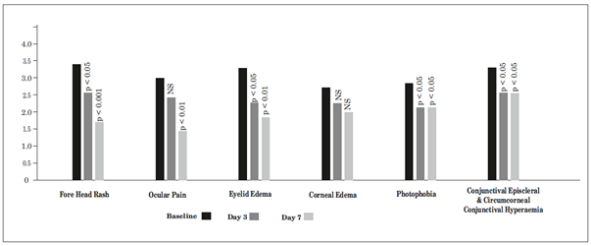

Figure 1. Ophthalmic Clinical Manifestations (n=7)

Table 2 Ophthalmic Clinical Manifestations (n=7)

Parameters	Base line		Day 3			Day 7		
	Mean	± S.D	Mean	± S.D	P-Value	Mean	± S.D	P-Value
Forehead/ Rash	3.42	0.78	2.57	0.53	P<0.05	1.7	0.75	P<0.001
Ocular pain	3.0	1.0	2.42	0.78	NS	1.42	0.53	P<0.01
Eyelid edema	3.28	0.95	2.28	0.48	P<0.05	1.85	0.9	P<0.01
Corneal edema	2.71	1.11	2.28	0.95	NS	2	0.81	NS
Photophobia	2.85	0.9	2.14	1.21	P<0.05	2.14	1.21	P<0.05
Conjunctival episcleral & circumcornea l conjunctival hyperaemia	3.28	0.95	2.57	1.27	P<0.05	2.57	1.27	P<0.05

Severe ocular manifestations were recorded in 11 patients out of 30 patients. None of the patients had choroiditis, exophthalmos, scleritis, necrotizing scleritis nor glaucoma. Four patients had deep keratitis on day 1 and on day 3 it resolved in one patient and on day 7 it resolved in all the 4 patients. Keratic precipitates and synechia were present in one patient on day 1 and it resolved completely by day 3. Optic neuritis was present on day 1 and continued on day 3 and resolved by day 7.

Non severe ocular manifestations were recorded in 11 patients out of 30 patients. Inflammation of conjunctiva was present in 10 patients on day 1 and it resolved in 2 patients on day 3 and in 7 patients on day 7. Punctate epithelial keratopathy was present in 7 patients and it resolved in 2 patients on day 3 and another 3 patients on day 7. Episcleritis was present in 4 patients on day 1 and resolved completely on day 3 in all the patients.

Clinical Outcome : As clinical data is available for eleven patients and putting together the cure and improvement taken as success – the treatment was successful in all the patients treated.

Safety: Out of 11 patients, 8 patients had nausea, 2 had headache. Gastro intestinal intolerance, itching and abdominal cramps was noted in one patient each. The number of events were 13 reported by 11 patients. The intensity of the adverse event in two patients was moderate and rest of the nine patients it was mild, however the adverse events resolved completely in all the patients. None of the adverse events lead to the withdrawal of patient from the study. All the patients tolerated the study medication well. (Table 3)

Table 3 Adverse reactions (n=11)

S.No	Name of Adverse event	Number of Patients
1	Nausea	8
2	Headache	2
3	GI intolerance	1
4	Itching	1
5	Abdominal cramps	1

Global Evaluation is available for 26 patients as shown in the Table-4

Table 4 Global evaluation

(n=26)	Excellent	Very good	Good
Patient global evaluation	3(11.54%)	15(57.70%)	8(30.76%)
Doctor global evaluation	6(23.10%)	11(42.3%)	9(34.60%)

Compliance:

Overall compliance as measured by pill count was more than 75%.

Discussion:

Ocular herpes had potentially serious long term complications if left untreated, apart from being irritating and frustrating condition to suffer from[4].No effective treatment exists apart from artificial tears, topical antihistamines or cold compresses. Topical antibiotics are not indicated as they may lead to delay in the diagnosis of other possible ocular diseases[5].

Anti viral medications such as acyclovir, valacyclovir and Famciclovir are very effective in preventing the ocular involvement when begun within 72 hours after onset of the rash. Aciclovir has been shown to be effective in the treatment of ocular herpes. However, its dosing regimen and poor bioavailability has lead to difficulties with compliance. Famciclovir with its convenient dosing, unique pharmacokinetics and proven efficacy in treating uncomplicated ocular herpes was highly effective in the present study[2].

Ocular pain and Photophobia were present in all the patients as the presenting symptom and consistent with the literature, significantly reduced by day 7[4]. Conjunctival episcleral and circumcorneal conjunctival hyperaemia as reported by Shaikh S et al. resolved significantly at the end of 7 days. Optic neuritis is reported to be present in one in 400 patients and may proceed retinal disease or follow acute herpes zoster opthalmicus infection, however in the present study one patient had optic neuritis and it resolved completely on day 7[3].

Cobo LM et al. have reported keratic precipitates reduced in incidence by acyclovir treatment, similarly keratic precipitates one of the severe ocular manifestation was present in one patient in our study and it resolved completely on day 3 with famciclovir treatment[6].

Punctate epithelial keratopathy was persisting in two patients at the end of 7 days as mentioned by Shaikh S et al. that these lesions probably contain live virus and may either resolve or progress to dendrite formation. It was also stated that episcleritis may be localized or diffuse with pain and swelling as seen in 4 patients at baseline and resolved completely on day 3[3].

The risk of superimposed bacterial infection and rare complications like scarring may also be associated with ocular herpes, however in our study famciclovir was effective in controlling and preventing these complications[4].

Conclusion:

In this present open label, non – comparative, non-randomized study, tablet Famciclovir 500 mg (PENVIR) three times a day for 7 days, was found to be effective in decreasing the symptoms of Ocular herpes and preventing the ocular complications. The study medication was tolerated well with minimal adverse events. The treatment was successful in all the patients treated with the study medication.

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