Research Article

PHARMACOKINETICS EVALUATION OF ACYCLOVIR IR 200 MG CAPSULE FORMULATIONS IN HEALTHY INDIAN ADULT VOLUNTEERS UNDER FASTING AND NON-FASTING CONDITIONS

P Susantakumar[1], Ajay Gaur[2] and Piush Sharma[3]
[1] Department of Pharmaceutical Sciences, Singhania University, Rajasthan, India.
[2] Associate Professor, L.M. College of Sc. & Tech. (Pharmacy), Jodhpur, India.
[3] Assistant Professor, Maharisi Arvind College of Pharmacy, Amabari, Jaipur, India .
*Corresponding author's E-mail: susanta03@yahoo.co.in

ABSTRACT

This study aimed to compare the systemic pharmacokinetics evaluations of test acyclovir IR 200mg capsule formulation compared with reference drug (Zovirax® 200mg IR Capsule), in healthy volunteers under fasting and non-fasting conditions with a single-dose, randomized, 2-period crossover study in healthy Indian adult volunteers, each subject received a single oral dose of either test or reference formulation followed by a 7-day washout period under fasting and non-fasting conditions. A serial of blood samples were collected over a period of 24 hours and plasma was separated and analyzed for acyclovir concentration using a validated LC-MS/MS liquid chromatography method with a lower limit of quantification of 5.0ng/mL. The formulations were to be considered bioequivalent if the log-transformed ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were within the predetermined bioequivalence range of 80% to 125%. There were no significance difference of mean values of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max} and $t_{1/2}$ following administration of the test and reference product for fasting and non-fasting conditions. No significant differences were found based on analysis of variance, with mean values and 90% confidence intervals of test/reference least square mean ratios for these parameters as follows: Cmax, 99.19% (95.09-107.86) versus 97.73% (92.27-110.89); AUC0-t, 99.13% (96.27-103.51) versus 98.75% (98.81-112.11); and AUC0-∞, 97.18% (92.88-100.94) versus 99.75% (99.07-114.60) ng.hr/mL under fasting versus non-fasting conditions, respectively. No serious adverse events were recorded, and there were no clinical significant changes in vital signs, clinical laboratory variables, ECG parameters or physical examination findings in both fasting and non-fasting study. In these healthy Indian volunteers, results suggested that the test and reference formulations of Acyclovir IR 200 mg capsules were within the acceptable range of 80 and 125 and bioequivalent, based on the regulatory definition under fasting and non-fasting conditions. Food did not significantly affect the C_{max} or AUC_{0-t} or $AUC_{0-\infty}$ of acyclovir between test and reference products and were well tolerated.

Keywords: Acyclovir, Pharmacokinetics, Bioequivalence.

INTRODUCTION

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2)[1-7], and varicella-zoster virus (VZV)[8-13]. The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. Acyclovir became the drug of choice for the treatment of HSV and VZV infections, particularly primary and recurrent genital herpes and mucocutaneous HSV[2-7,12] and VZV infections in immunosuppressed patients.[5-14]

Absorption of acyclovir from the gastrointestinal tract is variable and incomplete; 10–30% of an oral dose may be absorbed.[15-18] Peak plasma concentrations usually are attained within 1.5–2.5 hours after oral administration.[15-16]. The average oral bioavailability of acyclovir is 10-20%, which decreases with increasing dose. Food does not appear to affect GI absorption.[15, 18] Approximately 80% of an oral dose is never absorbed and is excreted through the faeces. Metabolized partially to 9-carboxy methoxy methylguanine also converted intracellularly in cells infected with herpesviruses to acyclovir triphosphate, the pharmacologically active form of the drug.[18,19] Excreted principally in urine as unchanged drug with initial serum half-life averages 0.34 hour and terminal half-life

averages 2.1–3.5 hours. The plasma half-life of oral acyclovir on average is 3 hours in adults with normal renal function.[15, 20]

Because of incomplete and variable absorption of acyclovir following oral administration, studies of the pharmacokinetics and tolerability of a newly developed formulation of this drug are essential. The objective of this study was to compare the bioequivalence and tolerability of acyclovir from a new test capsule 200mg immediate release formulation with that of a reference product (Zovirax®, GlaxoSmithKline, UK).

MATERIALS AND METHODS

Materials

The ingredients used for test capsule formulation were: micro-crystalline cellulose (Avicel® PH101), sodium starch, a lactose, magnesium stearate and sodium lauryl sulfate, FD&C Blue No. 2 and titanium oxide and reference product was 200-mg Zovirax® Capsule.

Methods

In Vitro Dissolution Study:

Dissolution of the test and reference product was conducted by the USP II method (paddle apparatus) at 50 rpm, with medium volume 900 mL, i.e. 0.1 N HCl (pH

2.2), phosphate buffer pH 4.5, acetate b u f f e r p H 6.8 and deionized water (pH approx. 5.5) as the dissolution medium at 37 ± 5°C. The UV absorbance was measured at 260 nm. For each dissolution profile, one capsule was added to the medium and samples of the medium were drawn at 5, 10, 15, 20, 30 and 45 min (n = 12 per product).

Subjects Participant

The study protocol followed the guidelines of the Helsinki Declaration 2008 and study was approved by the institutional ethics committee. All the subjects provided written informed consent to participate in the study prior to enrolment and were free to withdraw at any time during the study. Total thirty six healthy volunteers (18 male and 18 female) were scheduled to participate in each fasting and non-fasting study. All subjects were undergoing a screening procedure at least 21 days before the first day of dosing Subjects were eligible to participate if they were >18 years of age and were determined to be in good health as assessed by history, physical examination, and laboratory studies including serum chemistries, complete blood count with differential, and 12-lead electrocardiogram. Subjects were excluded if they had histories of a major disease of the kidneys, the liver, or the cardiovascular system at screening. Sample size is based on estimates obtained from reported literature/ previous pilot study.

Study Design

The study was designed as open-labeled, balanced, randomized, two-treatment, two-sequence, two period, single dose, crossover bioequivalence study with 7 days washout period. Thirty six subjects were randomized and divided into two equal groups and assigned to one of the two sequences of test or reference product administration. All subjects were fasted overnight atleast 10 hour before dosing in fasting condition and 30 minutes before beginning of standard high-fat breakfast (800-1000cal). Each subject received a single dose of single 200-mg capsule of either formulation with 240 mL of water and continued fasting for 4 hours. The subjects were allowed to ingest water *ad libitum* after 2 hours of doses and identical, nutritionally balanced meals were provided to all subjects during the remainder of the study period. Blood samples of 5.0mL each was drawn at 0.00, 0.333, 0.667, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00 and 24.00 hours were collected after dosing and centrifuge at 4000 rpm for 10 minutes at 4°C. The plasma samples were separated and stored at or below -20°C till analysis.

Method of Plasma Sample Analysis

The analytical method used for determination of drug concentrations in *in-vitro* plasma samples was a validated LC-MS/MS liquid chromatography method with Mass spectrometer detection mode. The assay method involves a solid phase extraction and chromatographic separation on a Hypersil GOLD C_{18}, 4.6 x 50 mm, 5µi.d (Thermo Electron Corporation) column using a gradient detection. The calibration curves of acyclovir were linear in the range of 5.0 ng/mL to 5000 ng/mL, with a lower limit of quantification at 5.0 ng/mL and correlation >0.99980 (r^2 value). The lower limit of quantization and limit of detection were 5.0ng/mL and 30ng/mL, respectively. The mean absolute recoveries of acyclovir from plasma were ranged from 97.3-105%.[21-24]

Pharmacokinetics and Statistical Analysis:

Pharmacokinetic parameters (C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, and k_{el}) were calculated by non-compartmental analysis using WinNonlin pharmacokinetic software. The statistical analyses of pharmacokinetic parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) were performed by using the SAS® software. The test the bioequivalence of the test and reference formulation, analysis of variance (ANOVA) for the crossover design was conducted on log-transferred C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Ratios of the geometric means of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ as well as 90% confidence intervals (CIs) were calculated. The formulations were to be considered bioequivalent if the log-transferred ratios (test/reference) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the predetermined bioequivalence range of 80% to 125%. The comparative dissolution profile of test and reference product was calculated at 5% significance level.

RESULTS

In Vitro Dissolution tests:

The dissolution behaviors of acyclovir test and reference product dissolved quicker in 0.1N HCL, phosphate buffer pH 4.5, and acetate buffer pH 6.8 medium were 91.15%, 89.65% and 86.19% in 30 minutes, respectively, which was more than or equal to 85% of drug substance is released within 30 minutes.[50, 51] The dissolution results exhibited that the release profiles of test and reference product acquired were similar across the different dissolution media (both fasted and non-fasted state) indicating their robustness of release characteristics in the different conditions extant in the upper GI tract milieu. The mean cumulative percent of acyclovir dissolved using 0.1N HCL as the dissolution medium for test and reference capsules are results were shown in Figure 1.
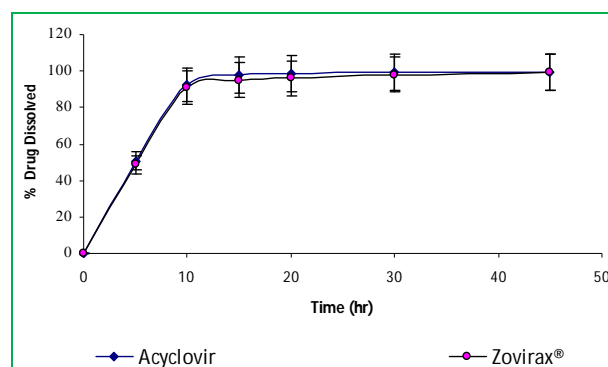

Figure 1: Mean ±SD cumulative percent of acyclovir dissolved using 0.1N HCL as the dissolution medium for test and reference capsules. Each data point is the mean data for 12 capsules.

Subjects Participants:

Demographic information for all subjects enrolled in the fasting and non-fasting study is presented in Table 1. Thirty six subjects was enrolled and completed both periods in each fasting and non-fasting study. Total thirty-six (36) data sets were analyzed for the efficacy evaluation for fasting and non-fasting study.

Pharmacokinetic analysis

Both formulations of acyclovir were readily absorbed from the gastrointestinal tracts of the volunteers. The mean concentration-time curves of test and reference products, each administered as a single 200 mg oral dose to 36 healthy Indian volunteers in fasting and non-fasting study are shown in the Figure 2 and 3 respectively. The primary pharmacokinetic parameters for test and reference products are listed in Table 2. Under non-fasting conditions, variability in absorption of acyclovir was small (Table 2) and insignificant ($p>0.05$) and mean acyclovir of pharmacokinetic parameters (e.g., C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$) results were reproducible (Figure 3). With the bioequivalence criteria, food did not significantly affect the C_{max} or AUC_{0-t} or $AUC_{0-\infty}$ under fasting and non-fasting conditions respectively. The mean (±SD) C_{max}, T_{max}

and $t_{1/2}$ values of the test formulations were 466.413 (±219.629) ng/mL, 1.840 (±0.681) hr, 4.852 (±2.960) hr and reference formulations were 470.205 (±236.234) ng/mL, 1.705 (±0.638) hr and 5.755 (±3.664) hr respectively for fasting study. The mean (±SD) C_{max}, T_{max} and $t_{1/2}$ values of the test formulations were 459.107 (±112.111) ng/mL, 1.764 (±1.500) hr, 5.779 (±2.625) hr and reference formulations were 469.762 (±169.495) ng/mL, 1.792 (±1.267) hr and 4.917 (±1.588) hr respectively for non-fasting study.
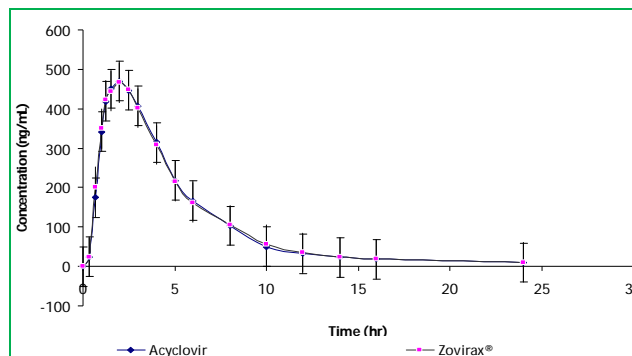

Figure 2: Mean ± SD Plasma concentration-time profile of acyclovir following oral administration of Test and Reference product over 24 hr under fasting conditions

Table 1: Demographic profile of subjects participated in both fasting and non-fasting study

Study Type	Gender, N	Age[1] Mean ± SD	Range	Body weight[1] (Kg) Mean ± SD	Range	Height[1] (cm) Mean ± SD	Range	BMI[1] (Kg/m^2) Mean± SD	Range
Fasting (N=36)	Male, 18	33.33 ± 4.83	41-26	55.37 ± 9.18	44.60-71.20	158.59 ± 12.25	142.00-77.30	21.91 ± 1.56	18.50-23.55
	Female, 18	32.44 ± 6.37	22-41	60.26 ± 7.45	46.90-69.34	165.29 ± 7.78	149.80-78.90	21.99 ±1.58	18.26-24.40
Non-fasting (N=36)	Male, 18	33.94 ± 4.66	26-40	55.43 ± 7.26	44.60-69.80	156.56 ± 8.53	19.08-24.76	22.53 ±1.33	19.08-24.76
	Female, 18	32.78 ± 5.97	22-42	57.75 ± 9.75	35.30-57.75	165.31 ± 8.72	149.80-78.90	21.09 ± 2.75	12.76-23.49

SD: Standard Deviation; N= Number of Subjects; [1]Determined at Screening

Table 2: Pharmacokinetic parameters of acyclovir under fasting and non-fasting conditions

Pharmacokinetic Parameters	Geometric mean ± SD (CV%)			
	Fasting Condition (N=36)		Non-Fasting Condition (N=36)	
	Acyclovir	Zovirax®	Acyclovir	Zovirax®
C_{max} (ng/mL)	466..413 ± 219.629 (42.53)	470.205 ± 236.234 (45.41)	459.107 ± 112.111 (24.53)	469.762 ± 169.495 (36.31)
AUC_{0-t} (ng.hr/mL)	2294.213 ±1063.874 (46.37)	2314.233 ±1084.339 (46.86)	2619.264 ± 676.220 (23.16)	2652.381 ± 890.312 (31.21)
$AUC_{0-\infty}$ (ng.hr/mL)	2393.577 ±1062.647 (44.18)	2463.012 ±1043.573 (42.37)	2901.077 ± 669.992 (21.61)	2908.437 ± 908.428 (30.20)
T_{max} (hr)	1.840 ± 0.681 (37.00)	1.705 ± 0.638 (37.45)	1.764 ± 1.500 (39.85)	1.792 ± 1.267 (38.49)
K_{el} (1/hr)	0.139 ± 0.068 (48.92)	0.143 ± 0.084 (58.96)	0.138 ± 0.048 (34.35)	0.140 ± 0.081 (33.31)
$T_{1/2}$ (hr)	4.852 ± 2.960 (72.39)	5.755 ± 3.664 (78.96)	5.779 ± 2.625 (45.42)	4.917 ± 1.588 (32.30)

Table 3: Summary statistics results of acyclovir in subjects under fasting and non-fasting conditions

Parameters	Product	Fasting study C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	Non-fasting study C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)
Geometric Mean	Test (A)	466.413	2294.213	2393.577	459.107	2619.264	2901.077
	Reference(B)	470.205	2314.233	2463.012	469.762	2652.381	2908.437
Least Square Mean (LSM)	Test (A)	440.012	2164.352	2537.192	433.120	2471.004	2736.865
	Reference(B)	443.590	2183.239	2610.793	443.172	2502.246	2743.808
LSM Ration A/B %		99.19	99.13	97.18	97.73	98.75	99.75
90% Confidence Interval : A/B							
Lower Limit		95.09	96.27	92.88	92.27	98.81	99.07
Upper Limit		107.86	103.51	100.94	110.89	113.11	114.60
P – value (ANOVA) Period		0.6351	0.8704	0.1403	0.7738	0.8515	0.8989
Formulation		0.8071	0.9886	0.6634	0.1064	0.3372	0.3459
Sequence		0.0622	0.0527	0.0642	0.8233	0.9441	0.9423
Intra-subject Variability: (CV%)		12.75	07.31	08.40	23.37	17.08	18.43
Power (%)		99.99	100.00	100.00	98.93	99.98	99.93

Results for the extent of absorption, as determined from mean (±SD) AUC_{0-t} and $AUC_{0-\infty}$ values of the test formulation were 2294.2135 (±1063.874) ng.h/mL and 2393.577 (±1062.647) ng.h/mL and reference formulations were 2314.233 (±1084.339) and 2463.012 (±1043.573) ng.h/mL respectively under fasting conditions. The mean (±SD) AUC_{0-t} and $AUC_{0-\infty}$ values of the test formulation were 2619.264 (±676.220) ng.h/mL and 2901.077 (±669.992) ng.h/mL and reference formulations were 2652.381 (±890.312) ng.h/mL and 2908.437 (±908.428) ng.h/mL for non-fasting study respectively. The acyclovir IR formulation in fasting condition was more rapidly absorbed than non-fasting condition and was able to achieve much higher acyclovir exposures (Figure 3).
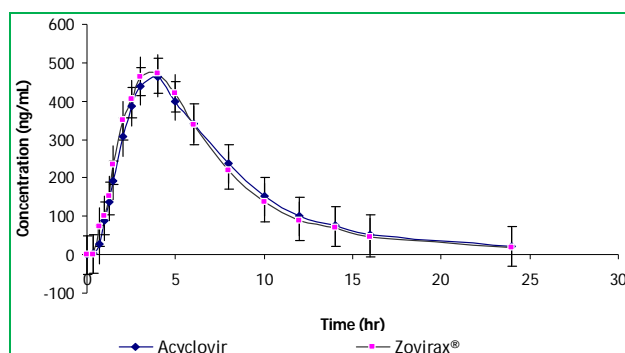

Figure 3: Mean ± SD Plasma concentration-time profile of acyclovir following oral administration of Test and Reference product over 24 hr under non-fasting conditions

On ANOVA, no period, formulation or sequence effects were observed for any PK property. The 90% confidence intervals of the ratios (test vs reference) for the natural log (ln)-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are shown in Table 3.

The ratio of the geometric means of the acyclovir pharmacokinetic characteristics C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, and the 90% CIs of test to reference products revealed insignificant (p>0.05) differences between the two products. The 90% confidence intervals for the ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 95.09 to 107.86, 96.27 to 103.51 and 92.88 to 100.94 respectively for fasting conditions and were 92.27 to 110.89, 98.81 to 113.11 and 99.07 to 114.60 respectively for non-fasting conditions. The 90% confidence Interval of the medium of the differences of t_{max} for both test and reference products were within significance ranges (p< 0.05) for fasting and within significance ranges (p<0.05) for non-fasting study of acyclovir. The data show that the point estimate and upper 90% CIs of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are the acceptable range and meeting the predetermined criteria for bioequivalence of 80% and 125% suggested by the FDA bioequivalence guideline.

DISCUSSION

Acyclovir is absorbed in the small intestine in a passive, variable and incomplete manner due its high hydrophilic nature.[25] Indeed, acyclovir has been replaced by its prodrug, valacyclovir, as a means of increasing systemic availability.[26] However, it is also possible to increase the oral absorption of acyclovir by improving the formulation.[26-30] This study examined the PK properties and bioequivalence of acyclovir - a new developed capsule 200mg formulation and an established brand capsule in healthy Indian adult volunteers under fasting and non-fasting conditions. Systematic review have found the rate of adverse events following its administration is not significantly different to that following administration of reference products in both fasting and non-fasting conditions.[17-19, 23]

The present bioequivalence study in healthy volunteers showed that the test capsule formulation of acyclovir produces higher plasma concentrations than the reference capsule. The point estimate and upper 90% CIs of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the acceptable range of 80 and 125 in both fasting and non-fasting conditions. The study results revealed that the two formulations of acyclovir were similar in PK characteristics among these healthy Indian volunteers. The mean C_{max} and $t_{1/2}$ obtained in this study for the test formulation, which was comparable to that of the reference formulation in both fasting and non-fasting conditions.[15, 18] The pharmacokinetic values for acyclovir from Zovirax® capsules obtained in this study were in good agreement with those from other studies.[21-24]

There were few adverse events were reported during the fasting and non-fasting study. The most frequently reported AEs after acyclovir treatment were itching, nausea, headache, dizziness and sleepiness; incidence of these AEs appeared to be dose-related[18]. All were mild in intensity and resolved without sequel. Post study safety analysis reports showed ALT and AST clinically significant abnormal Laboratory values which follow on repeat analysis were found to be normal. All the clinically significant abnormal lab values were remotely related to the study medication. In few incidences in which increase and decrease the blood pressure but there were not clinical significant changes in vital signs, clinical laboratory variables, ECG parameters or physical examination findings in both fasting and non-fasting study. All AEs reported for acyclovir were consistent with similar events in subjects treated with fasting and non-fasting condition. As far as this study is concerned, both the test and the reference formulations were well tolerated.

CONCLUSION

In this study in healthy Indian adult volunteers, a single 200 mg dose of the test acyclovir capsule formulation met the regulatory criteria for bioequivalence to a single 200 mg dose of the established reference 200mg capsule product based on the rate and extent of absorption under both fasting and non-fasting conditions. Both test and reference products were safe and well tolerated.

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