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COMMUNICATION

Bioavailability and Pharmacokinetics of Acyclovir Tablet Preparation

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ABSTRACT

The bioavailability of a generic preparation of acyclovir (Avorax) was compared with the innovator product, Zovirax. Twelve healthy volunteers participated in the study, conducted according to a randomized, two-way crossover design. The preparations were compared using the parameters area under the plasma concentration–time curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), and time to reach peak plasma concentration (T_{max}). No statistically significant difference was observed between the T_{max} or the logarithmic transformed $AUC_{0-\infty}$ and C_{max} values of the two preparations. In addition, the 90% confidence interval for the ratio of the logarithmic transformed $AUC_{0-\infty}$ values of Avorax over those of Zovirax was found to lie between 0.85 and 1.06, while that of the logarithmic transformed C_{max} values was between 0.95 and 1.25, being within the bioequivalence limit of 0.80–1.25. Moreover, the elimination rate constant (k_e), elimination half-life ($t_{1/2}$), and apparent volume of distribution (V_d) values obtained with the two preparations were comparable and not significantly different statistically.

INTRODUCTION

Acyclovir is a guanine derivative with strong antiviral activities against herpes viruses, particularly herpes simplex type 1 and 2, but relatively less effective against varicella zoster virus (1). When administered orally, only 15–30% of the dose was absorbed attributable to its poor solubility (2). Acyclovir is popularly prescribed and recent expiry of its patent has prompted manufacturing of generic versions of the drug. However, it is essential that the generic preparations are proven to be bioequivalent to the innovator preparation before they can be safely used as a substitute for the latter.

Therefore, in the present study, the bioavailability of a local generic preparation of acyclovir, Avorax, was evaluated in comparison with the innovator preparation, Zovirax. In addition, an attempt was also made to study the pharmacokinetics of acyclovir in the local population

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of Asian origin, which hitherto have not been investigated.

MATERIALS AND METHODS

Products Studied

Avorax tablets, 200 mg (Xepa-Soul Pattinson Manufacturing, Malaysia), batch no. 4241, manufacturing date 5/1996, expiry date 5/1999, were used.

Zovirax tablets, 200 mg (Wellcome Foundation, UK), lot no. H2311A, manufacturing date 3/1995, expiry date 3/2000, registration no. PBKD/860860, were used.

Acyclovir standard was obtained from Chemio Pharm, Milano, Italy.

Study Design

The study protocol was approved by an ethics committee. Twelve healthy adult male volunteers between 22 and 45 years old (mean = 35 years, SD = 8 years) and weighing from 54 to 78 kg (mean = 67 kg, SD = 7 kg), participated in the study after providing written informed consent. All were judged to be healthy and were not receiving any medication during the study period. The protocol used was a conventional, two-way, split groups, crossover study with six subjects in each of the two treatment groups and a washout period of 1 week. The volunteers were randomized to receive two tablets (400 mg) of Zovirax or Avorax. Both preparations were administered with 150 ml of water in the morning at 10:00 a.m. after a 12-hr overnight fast. Food and drinks were withheld for at least 2 hr after dosing. Lunch and dinner comprising chicken with rice were served at 4 and 9 hr after dosing and water was given *ad libitum*. Blood samples of 5 ml volume were collected in vacutainers (containing sodium heparin as anticoagulant) at 0 (predose), 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 18, and 24 hr after dosing. The blood samples were centrifuged for 15 min at 3500 rpm and the plasma transferred to separate glass containers to be kept frozen until analysis.

Analysis of Plasma Acyclovir Concentration

The plasma samples were analyzed using a reversed-phase high-performance liquid chromatographic (HPLC) method described by Peh and Yuen (3).

Pharmacokinetic Analysis

The two preparations were compared using the parameters peak plasma concentration (C_{max}), time to reach peak plasma concentration (T_{max}), and area under the plasma concentration-time curve ($AUC_{0-\infty}$), estimated from the plasma concentration–time profiles of the two preparations. Both C_{max} and T_{max} were obtained directly from the plasma date, while the $AUC_{0-\infty}$ was calculated by adding the area from time zero to the last sampling time t (AUC_{0-t}) and the area from time t to infinity ($AUC_{t-\infty}$). The former was calculated using the trapezoidal formula and the latter by dividing the last measurable plasma drug concentration with the elimination rate constant (k_e). The k_e was estimated from the terminal slope of the plasma concentration–time curve after logarithmic transformation and application of linear regression (4). The elimination half-life ($t_{½}$) was calculated using $\ln 2/k_e$, and the apparent volume of distribution (V_d) as dose/($AUC_{0-\infty} \cdot k_e$). For each of the parameters, $AUC_{0-\infty}$, C_{max}, k_e, $t_{½}$, and V_d, the values obtained for the two preparations were analyzed statistically using an analysis of variance procedure appropriate for the study design (5). The $AUC_{0-\infty}$ and C_{max} values were logarithmically transformed prior to the statistical analysis. Conversely, the T_{max} values were analyzed using the Wilcoxon signed rank test for paired samples. A statistically significant difference was considered at $p < 0.05$.

RESULTS AND DISCUSSION

The mean plasma concentration-time curves of acyclovir obtained with Avorax and Zovirax are shown in Fig. 1. Although the peak plasma concentration of Avorax was observed to be relatively higher than that of the Zovirax, the two plots appeared to be almost superimposable. Both products achieved rapid absorption, producing peak plasma concentrations at approximately 1.2 hr after dosing, and no lag time in absorption was observed.

Table 1 gives the individual values of T_{max}, C_{max}, and $AUC_{0-\infty}$ obtained with Zovirax and Avorax. The mean T_{max} values for Avorax and Zovirax were 1.1 ± 0.4 hr and 1.4 ± 0.5 hr, respectively, and were not significantly different when analyzed statistically ($p = 0.1294$). Moreover, the values are in good agreement with those reported by other groups (6,7). Referring to

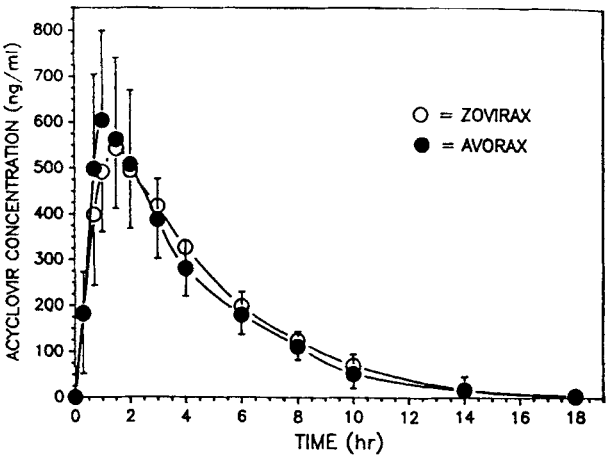

Figure 1. Mean plasma acyclovir concentration versus time curves of Avorax and Zovirax. Mean ± SD, $N = 12$.

Table 1, the mean C_{max} and $AUC_{0-\infty}$ values of Avorax appeared to be comparable to those of Zovirax. No statistically significant difference was obtained in the logarithmic transformed values of C_{max} ($p = 0.2915$) and $AUC_{0-\infty}$ ($p = 0.4502$) between the two preparations. In addition, the 90% confidence interval for the ratio of the logarithmic transformed $AUC_{0-\infty}$ values of Avorax over those of Zovirax was found to lie between 0.85 and 1.06, while that of the logarithmic transformed C_{max} values was between 0.95 and 1.25, being within the acceptable bioequivalence limit of 0.80–1.25 (8,9). On the basis of the results obtained from the above analysis, it can be concluded that the two preparations are comparable in both the rate and extent of absorption and therefore the two preparations are bioequivalent.

The numerical values of the pharmacokinetic parameters, k_e, $t_{½}$, and V_d of the two preparations are given in Table 2. The mean values of all the above parameters for both preparations were closely similar and were not significantly different statistically ($p = 0.5288$ for k_e, 0.9178 for $t_{½}$, and 0.6911 for V_d).

The $t_{½}$ values were found to vary between 1.6 and 5.5 hr, with a mean value of approximately 3.2 hr (Table 2), being comparable to those reported in the literature (10–13).

The mean V_d value obtained in the present study was approximately 9 liters/kg, being equivalent to 593 liters/1.73 m^2. This value was found to be larger (approximately 10 times) than those reported by other workers, where the drug was administered intravenously (10). This discrepancy can be explained by the difference in the route of administration used between the studies. The oral bioavailability of acyclovir has been reported to be only 15–30% (2). Since this was not taken into consideration during our computation of V_d using the relationship dose/$AUC_{0-\infty} \cdot k_e$, the values calculated are

Table 1

Numerical Values of T_{max}, C_{max}, and $AUC_{0-\infty}$

	Zovirax			Avorax		
Subjects	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (hr · ng/ml)	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (hr · ng/ml)
RV	2.0	505.4	2981.1	1.0	429.5	239.14
MY	1.5	596.0	2893.4	0.7	520.0	2297.3
AD	1.5	526.0	2359.9	1.0	709.2	2402.8
SF	1.0	623.0	2552.2	1.5	422.0	2207.4
MH	2.0	562.5	3418.9	1.0	537.6	2546.2
JY	2.0	730.9	5081.2	1.0	959.6	4320.7
JA	1.5	796.6	3257.1	1.0	617.8	2981.7
ZA	1.0	585.8	2812.0	2.0	866.3	3743.1
WA	1.5	527.1	2342.8	1.0	612.8	1988.5
AD	0.3	314.8	1891.3	1.0	524.5	2765.8
HA	0.7	706.2	3086.8	0.7	969.1	4293.5
YS	1.5	649.6	4554.0	1.0	709.4	3693.0
Mean	1.4	593.7	3102.5	1.1	656.5	2956.6
SD	0.5	125.2	913.9	0.4	190.5	840.4

Table 2

Numerical Values of k_e, $t_{1/2}$, *and* V_d

Subjects	Zovirax k_e (hr^{-1})	Zovirax $t_{1/2}$ (hr)	Zovirax V_d (liters/kg)	Avorax k_e (hr^{-1})	Avorax $t_{1/2}$ (hr)	Avorax V_d (liters/kg)
RV	0.3070	2.3	7.3	0.2858	2.4	10.4
MY	0.2823	2.5	9.1	0.2289	3.0	14.1
AD	0.2344	3.0	11.0	0.3898	1.8	6.5
SF	0.1986	3.5	11.3	0.2353	2.9	11.0
MH	0.1833	3.8	9.0	0.1885	3.7	11.7
JA	0.1274	5.4	7.9	0.1269	5.5	9.4
JF	0.2879	2.4	6.4	0.2292	3.0	8.7
ZA	0.2272	3.1	9.1	0.2418	2.9	6.4
WA	0.3673	1.9	6.0	0.4326	1.6	6.0
AD	0.2626	2.6	11.8	0.3044	2.3	7.0
HA	0.1860	3.7	10.3	0.1598	4.3	8.6
YU	0.1664	4.2	9.4	0.1451	4.8	13.3
Mean	0.1607	3.2	9.0	0.2473	3.2	9.4
SD	0.0414	1.0	1.9	0.0936	1.2	2.7

thus expected to be larger than when acyclovir was administered intravenously.

CONCLUSION

In conclusion, Avorax was found to be comparable to Zovirax in both the rate and extent of absorption. Moreover, the pharmacokinetic parameters, k_e, $t_{1/2}$, and V_d, estimated from administration of the two products were not significantly different and the $t_{1/2}$ values were comparable to those reported in the literature.

REFERENCES

1. D. I. Dorsky and C. S. Crumpacker, Ann. Intern. Med., 107, 859 (1987).
2. S. E. Straus, H. A. Smith, C. Brickman, P. de Miranda, C. McLaren, and R. E. Keeney, Ann. Intern. Med., 96, 270 (1982).
3. K. K. Peh and K. H. Yuen, J. Chromatogr. B., 693, 241 (1997).
4. M. Gibaldi and D. Perrier, in *Pharmacokinetics*, 2nd ed., Marcel Dekker, New York, 1982, p. 145.
5. J. G. Wagner, in *Fundamentals of Clinical Pharmacokinetics*, 1st ed., Drug Intelligence, Hamilton, IL, 1975, p. 285.
6. D. Brigden, A. Fowle, and A. Rosling, in *Developments in Antiviral Therapy* (L. H. Collier and J. S. Oxford, eds.), Academic Press, New York, 1980, p. 53.
7. R. B. Van Dyke, J. D. Connor, C. Wyborny, M. Hintz, and R. E. Keeney, Am. J. Med., 73 (Suppl), 172 (1982).
8. W. J. Westlake, in *Biopharmaceutical Statistics for Drug Development* (K. E. Peace, ed.), Marcel Dekker, New York, 1988, p. 329.
9. *The United States Pharmacopeia*, 23, Rockville, MD, 1995.
10. O. L. Laskin, Clin. Pharmacokinet., 8, 187 (1983).
11. S. A. Spector, J. D. Connor, M. Hintz, R. P. Quinn, M. R. Blum, and R. E. Keeney, Antimicrob. Agents Chemother. 19, 608 (1981).
12. O. L. Laskin, J. A. Longstreth, R. Saral, P. de Miranda, R. Keeney, and P. S. Lietman, Antimicrob. Agents Chemother. 21, 393 (1982).
13. P. de Miranda, R. J. Whitley, M. R. Blum, R. E. Keeney, N. Barton, D. M. Cocchetto, S. Good, G. P. Hemstreet, L. E. Kirk, B. S. Page, and G. B. Elion, Clin. Pharmacokinet. Ther., 26, 718 (1979).