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Valacyclovir Pharmacokinetics and Exploratory Pharmacodynamics in Young Adults With Epstein-Barr Virus Infectious Mononucleosis

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Abstract

Primary Epstein-Barr virus (EBV) infection often results in infectious mononucleosis and is associated with serious sequelae. No treatment is approved for EBV infection, and an antiviral intervention would be significant. The objectives of this study are to characterize the pharmacokinetics and explore the pharmacodynamics of acyclovir in plasma and oral washings of 8 subjects receiving 7 days of valacyclovir 1500 mg twice daily for EBV infectious mononucleosis. Virologic and clinical responses are assessed over 12 days. Acyclovir is measured by liquid chromatography/ultraviolet detection. EBV DNA is quantitated by TaqMan polymerase chain reaction. NONMEM VI and linear regression are used for data analysis. Acyclovir profiles in plasma and oral washings are consistent with a 1-compartment model. Final model estimates of clearance, volume of distribution, and fraction of acyclovir in oral wash supernatant are 49.9 L/h, 74.1 L, and 1.14%, respectively. The quantity of EBV DNA in oral washings and blood, and the severity of illness, measured by a graded scale, decrease during treatment. After treatment, viral rebound occurs in oral washings but not in blood, and the severity of illness continues to decline. Acyclovir pharmacokinetic parameters do not correlate with response metrics. These results support further studies of valacyclovir for EBV infectious mononucleosis.

Keywords

Valacyclovir; pharmacokinetics; pharmaco-dynamics; Epstein-Barr virus; infectious mononucleosis

Primary Epstein-Barr virus (EBV) infection in adolescents and young adults often results in infectious mononucleosis. This illness may cause loss of productivity for several months, especially among college students.¹ In addition, primary EBV infection has been associated

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with important sequelae in both immunocompetent and immunocompromised hosts.^{2–6} An antiviral drug that could reduce the severity of acute infectious mononucleosis and potentially lower the risk for serious sequelae would be highly desirable. Unfortunately, there is no approved treatment for EBV infectious mononucleosis, and the use of antiviral drugs is controversial. Data from early clinical trials with intravenous or orally administered acyclovir failed to demonstrate a clinical benefit of antiviral therapy but did show an anti-EBV effect.⁷ These findings may have been limited by the design of earlier studies or the acyclovir formulation and doses evaluated. More recently, our EBV research group showed that valacyclovir, the oral pro-drug of acyclovir with 3- to 5-fold greater bioavailability, had both an antiviral effect and a clinical benefit in university students with primary EBV infectious mononucleosis.⁸ This study prompted a formal evaluation of the clinical pharmacology of valacyclovir for the treatment of EBV infectious mononucleosis. Valacyclovir is rapidly and almost completely converted to acyclovir by first-pass metabolism following oral administration. Acyclovir undergoes minimal protein binding (ie, 13.5%–17.9%) and is primarily eliminated renally with a plasma elimination half-life of 2.5 to 3.3 hours in individuals with normal renal function.⁹

There are no published data on the pharmacokinetics or pharmacodynamics of antiviral drugs when used to treat an acute EBV infection. The objectives of this study were to characterize the pharmacokinetics of acyclovir in the plasma and oral washings of university students receiving valacyclovir 1500 mg twice daily for 7 days for the treatment of EBV infectious mononucleosis and to explore exposure-response relationships.

METHODS

Subjects

The study was conducted at the University of Minnesota in collaboration with the Boynton Student Health Service (BHS). The University of Minnesota Institutional Review Board approved the study, and written informed consent was obtained from each volunteer prior to screening. University of Minnesota students were eligible if they were 18 years of age or older, were symptomatic for 7 days or less and diagnosed with infectious mononucleosis, had IgM antibodies against EBV viral capsid antigen, and had a normal serum creatinine and estimated glomerular filtration rate. All female subjects had to have a negative urine pregnancy test at screening and agree to use effective contraception defined as either a barrier method or hormone administration during and for 30 days after completion of the study. Volunteers were excluded if they had a history of EBV infectious mononucleosis, had end-stage kidney or liver disease, were immuno-compromised because of an underlying medical condition, were taking chronic immunosuppressive or immunomodulating medications, or were receiving valacyclovir or acyclovir. Medications prescribed by the subject's primary provider for symptomatic management of the present illness were allowed and their usage was recorded.

Study Design

This was a prospective, open-label study conducted under FDA investigator-sponsored IND 68,519. Subjects were initially identified by their primary providers at the BHS and referred

to the Virology Research Clinic for the study. At the screening visit, subjects provided a detailed medical history, underwent a physical examination, and had blood samples drawn for EBV antibodies, quantitative EBV DNA (qEBV), a complete blood cell count with differential and platelets, serum creatinine, and alanine transaminase. Female subjects took a urine pregnancy test. An oral wash sample for qEBV was also obtained by having subjects gargle vigorously for 30 seconds with 20 mL of 0.9% normal saline.

Enrollment took place on or within 24 hours of the screening visit. At the enrollment visit or study day 1, subjects had blood samples drawn for EBV antibodies and qEBV. An oral wash sample for qEBV was obtained as previously described. A severity of illness scale for infectious mononucleosis was used to grade each subject's current state of health.¹⁰ Briefly, this scale consists of 2 categories, physical activity limitation and symptom/pain intensity, which are independently graded on a 0 to 3 scoring system. The severity of illness score is the sum of the evaluations of each of these categories. Scores range from 0 (completely asymptomatic) to 6 (essentially bedridden). Subjects received a 7-day supply of valacyclovir 1500 mg twice daily along with a medication adherence diary. This dose was chosen because it represented the highest total daily dose of valacyclovir approved by the US Food and Drug Administration for another herpes virus infection, herpes zoster, or shingles. In addition, it would provide acyclovir exposures above the in vitro concentration needed to inhibit EBV replication by at least 50% (IC₅₀).¹¹ A twice-daily dosing schedule was selected to assist with medication adherence among study subjects. Subjects were instructed to take their first valacyclovir dose in the evening; record the amount, date, and time of the dose in the diary; and repeat this documentation procedure for all subsequent doses. Medication adherence diaries and pill counts were assessed at each study visit during valacyclovir treatment.

Subjects made a total of 7 study visits over 12 days. On either study day 3, 4, or 5, subjects came to the General Clinical Research Center (GCRC) for a 12-hour pharmacokinetic visit. Subjects arrived at the GCRC after an overnight fast, had a saline lock placed in one arm to obtain serial venous blood samples for plasma acyclovir concentrations, and received a standardized breakfast (641 kcal; 5.1% protein, 12.7% carbohydrates, 3.4% fat). Following breakfast, each subject had a pre-dose (time = 0) blood sample drawn and took an observed dose of their valacyclovir with 8 oz of water. Additional blood samples were drawn at 1, 2, 4, 6, 8, and 12 hours post-dose. Oral wash samples for acyclovir concentrations were obtained as previously described at these same time points. The blood and oral wash samples collected at time 0 and 12 hours post-dose were also used for qEBV. In addition to the 12-hour pharmacokinetic visit, each subject had 4 other study visits during valacyclovir treatment and 2 study visits after treatment was completed. At each on-treatment study visit, a blood sample and an oral wash sample were collected for acyclovir concentrations and qEBV. At each post-treatment study visit, a blood sample and an oral wash sample were obtained for qEBV only. Medication adherence diaries were collected at each subject's final study visit.

Safety Evaluations

Safety was assessed at each study visit by conducting physical examinations, measuring vital signs, grading the severity of EBV infectious mononucleosis, and recording adverse events. Adverse events were graded using the Division of Acquired Immunodeficiency Deficiency Syndrome, National Institute of Allergy and Infectious Diseases, National Institutes of Health Table for Grading the Severity of Adult and Pediatric Adverse Events. At the final study visit, all subjects had a blood sample drawn for a complete blood cell count with differential and platelets, serum creatinine, and alanine transaminase. Female subjects underwent a second urine pregnancy test within 30 days of study completion.

Quantitation of Acyclovir in Plasma and Oral Wash Samples

Plasma concentrations of acyclovir were measured using a validated reversed phase high-performance liquid chromatography assay. Plasma (200 μ L) was subjected to protein precipitation with perchloric acid. A 25- μ L volume of pH-adjusted protein free extract was injected. The mobile phase consisted of 97.5% 25 mM phosphate buffer (pH 6) and 2.5% acetonitrile (vol/vol). The stationary phase was a 3 $\times$ 150-mm YMC C4 reversed phase column. The flow rate was 0.4 mL/min with detection at 266 nM. All analytic measurements were performed using an HP series 1100 LC system (Agilent Technologies, Palo Alto, Calif). The assay internal standard was dideoxycytidine. Plasma standards ranged from 25 to 10 000 ng/mL. Accuracy and variability were determined using 4 quality controls (25, 75, 750, and 7500 ng/mL) measured in triplicate on 5 separate days. A single-factor analysis of variance (ANOVA) was used for statistical analysis. Accuracy ranged from 97.4% to 106.6%. Within and between assay variability, expressed as a coefficient of variation (CV %), ranged from 0.4% to 3.3% and 0.8% to 5.3%, respectively.

All oral washes were centrifuged at 600 *g* for 10 minutes to separate the sample into supernatant and cell pellet fractions. Acyclovir concentrations were determined in the supernatant fraction only using a modified version of the acyclovir plasma assay described above. Oral wash fluid-derived supernatant (200 μ L) was first combined with 200 μ L of 5% N- acetylcysteine and then sonicated for 30 minutes. The solution was extracted with 2 mL of dichloromethane-isopropyl alcohol (1:1, vol/vol), similar to the method by Bahrami et al.¹² Dried extract was reconstituted in mobile phase and 25 μ L was injected. The mobile phase consisted of 96.0% 25 mM phosphate buffer (pH 7) and 4.0% acetonitrile (vol/vol). The stationary phase was a 4.6 $\times$ 250-mm Waters Spherisorb C8 reversed phase column. The flow rate was 0.5 mL/min with detection at 266 nM. All analytic measurements were performed using the HP system described previously. The assay internal standard was dideoxycytidine. Oral wash fluid-derived supernatant standards ranged from 2 to 1000 ng/mL. Quality controls at 5 and 500 ng/mL were assayed in duplicate on 3 separate days. A single-factor ANOVA was used for statistical analysis. Accuracy ranged from 100.0% to 104.3%. Within- and between- assay variability, expressed as CV%, ranged from 7.5% to 7.9% and 6.4% to 10.5%, respectively.

Quantitation of EBV DNA in Whole Blood and Oral Wash Samples

The qEBV assays were performed on the oral wash fluid-derived supernatant, reconstituted oral cell pellet, and whole blood as reported previously.¹⁰ The amplicon for our qEBV assay

was a 71-base pair portion of the *EBNA-1* gene. The forward primer was 5'-GAC TGT GTG CAG CTT TGA CGA T-3'; the reverse primer was 5'-CGG CAG CCC CTT CCA-3'; and the probe was 5'-(FAM) TAG ATT TGC CTC CCT GGT TTC CAC CTA TG – (TAMRA)-3'. Quantitative EBV data were expressed as viral copies per milliliter of whole blood or oral wash. The reliable limit of detection of the assay was 10 copies per reaction (coefficient of variation, 30%), which equates to 40 copies/mL for the oral wash fluid-derived cell pellet and 1000 copies/mL for the oral wash fluid-derived supernatant and the whole blood.

Pharmacokinetic Analysis

Acyclovir concentration-time data in the plasma and oral wash fluid-derived supernatant were combined and analyzed simultaneously using a nonlinear mixed-effects modeling approach to determine the pharmacokinetic parameters of acyclovir in these biologic matrices. Doses for valacyclovir were recorded as milligrams of valacyclovir and not corrected for molecular weight differences between acyclovir and valacyclovir. The model estimated parameters, apparent oral clearance (CL/F) and apparent volume of distribution (V/F), implicitly accounted for this difference through the bioavailability (F) term.

NONMEM version VI, level 1.0 with PDxPOP version 3.0 (LLC, Globomax, Ellicott City, Md), and Compaq (Digital) Visual Fortran 6.0 Compiler (Houston, TX) were used for data analysis.¹³ Oral doses of valacyclovir were administered into an absorption depot compartment. Absorption of valacyclovir was modeled as a first-order process, and conversion to acyclovir in the central compartment was assumed to be instantaneous. A 1-compartment model with first-order elimination for acyclovir disposition in plasma was specified with ADVAN2 and TRANS2. The model was parameterized in terms of CL/F, V/F, and absorption rate constant (K_a). Acyclovir concentrations in the oral wash fluid-derived supernatant were initially hypothesized to be a constant fraction of the modeled plasma concentrations. This fraction in the oral wash fluid-derived supernatant (F_{sup}) was estimated simultaneously with the acyclovir pharmacokinetic parameters.

Between-subject variabilities on CL, V, and F_{sup} were modeled using a proportional error model. This imposed a log-normal distribution on the parameters with the results expressed as a coefficient of variation. Residual unexplained variability was estimated for the acyclovir plasma concentrations (RUV_{pl}) and oral wash fluid-derived supernatant (RUV_{sup}) separately. In both cases, the RUV was assumed to have a log-normal distribution and was also expressed as a coefficient of variation. The estimation method implemented for all runs was the first-order conditional estimation with interaction (FOCE-I) method. Four significant figures were specified for the estimation procedure.

Metrics of Exposure and Response

Acyclovir exposure metrics of interest were the area under the concentration-time curve in plasma (AUC_{pl}) and the AUC in oral wash fluid-derived supernatant (AUC_{sup}). These metrics were derived from the empirical Bayes estimates of individual pharmacokinetic parameters.

Metrics of both virologic and clinical pharmacodynamic response to acyclovir were available for exploratory analyses. The rate of viral load reduction in the oral wash fluid-derived supernatant, oral wash fluid-derived cell pellet, and the whole blood approximated a first-order process and the rate constants of viral load versus study day to the last on-treatment study visit were calculated using KaleidaGraph data analysis software (version 4.03, Synergy Software, Brentwood, Tenn). The half-life of EBV DNA decay in each biologic matrix was calculated as $\ln(2)/K$. The cumulative exposure to EBV DNA in the oral wash fluid-derived supernatant, the oral wash fluid-derived cell pellet, and the whole blood during the treatment period was calculated as an area under the viral load–time curve using the linear trapezoidal rule. Measures of clinical response included the half-life of the severity of illness score and the cumulative severity of illness score from enrollment to the last on-treatment study visit and were computed as above for each subject.

Exposure-Response Relationships

Relationships among acyclovir exposure and the various pharmacodynamic metrics were explored by visual inspection and linear regression analysis using KaleidaGraph data analysis software (version 4.03; Synergy Software, Reading, PA). Although a *P* value of less than .05 in a regression analysis indicates that a slope is significantly different from zero, it might poorly capture important nonlinear (eg, U-shaped) relationships. Therefore, visual inspection of the relationships, although empirical, was given prominence in these exploratory analyses.

Additional Statistical Considerations

A sample size of 8 subjects was deemed adequate to characterize the pharmacokinetic parameters for acyclovir after oral administration of valacyclovir and to explore potential pharmacodynamic relationships. No formal statistical tests or sample size calculations were performed. All demographic, pharmacokinetic, pharmacodynamic, and safety data were summarized descriptively.

RESULTS

Study Population

Nineteen subjects were screened for the study, 11 subjects did not meet the eligibility criteria, and 8 subjects with EBV infectious mononucleosis were enrolled and included in the pharmacokinetic and safety analyses. Seven subjects with primary EBV infection were included in the pharmacodynamic analysis. One subject with recurrent or nonprimary EBV infectious mononucleosis was excluded. The median (range) baseline subject characteristics are summarized in Table I.

Acyclovir Pharmacokinetics

A total of 84 plasma samples and 64 oral wash fluid-derived supernatant samples were available for the determination of acyclovir and used in the pharmacokinetic analysis. The observed acyclovir concentration–time data for the plasma and the oral wash fluid-derived supernatant are presented in Figures 1a and 1b, respectively. All profiles were consistent with a 1-compartment pharmacokinetic model.

All parameter estimates and their relative standard errors (%) for the final model are shown in Table II. Plots of the observed concentrations versus the concentrations predicted under the regression model for plasma and oral wash fluid-derived supernatant are presented in Figures 2a and 2b, respectively. Standard diagnostic plots stratified by plasma and oral wash fluid-derived supernatant observations suggested that the model was adequate to describe the data. Median (range) acyclovir AUC_{pl} and AUC_{sup} were 29 900 (25 400–34 300) ng·L/h and 341 (289–391) ng·L/h, respectively.

Pharmacodynamic Evaluations

The half-lives of EBV DNA decay in the oral wash fluid-derived supernatant, oral wash fluid-derived cell pellet, and whole blood were 50.6, 17.0, and 60.3 hours, respectively. The median viral load in each biologic matrix as a function of study day is presented in Figure 3. One subject made her last study visit on study day 16 instead of study day 12. It was noted that all subjects experienced viral rebound in the oral wash fluid-derived supernatant and cell pellet after completing the 7-day course of valacyclovir. The median severity of illness score as a function of study day is shown in Figure 4. The severity of illness score did not rebound in any subject following treatment with valacyclovir. Acyclovir pharmacokinetic parameters (CL/F and V/F) and exposure metrics (AUC_{pl} and AUC_{sup}) did not correlate with any of the virologic response metrics in the oral wash fluid-derived supernatant, oral wash fluid-derived cell pellet, or whole blood or with the clinical severity of illness metrics over the treatment period.

Safety and Medication Adherence Findings

Valacyclovir 1500 mg twice daily for 7 days was well tolerated by all subjects in this study. One episode of mild (grade 1) nausea was reported and deemed possibly related to study medication. The subject's nausea occurred following the first dose of valacyclovir and resolved without intervention. Adherence to valacyclovir was also excellent. Among the 8 study subjects, there was only 1 missed dose identified through regular pill counts and review of medication adherence diaries.

DISCUSSION

Ours is the first study to characterize the pharmacokinetics and exploratory pharmacodynamics of acyclovir when valacyclovir 1500 mg every 12 hours is used for the treatment of EBV infectious mononucleosis. Both plasma and oral wash fluid-derived supernatant concentration-time data were combined into a single data set and used to estimate acyclovir pharmacokinetic parameters and exposure metrics. Our median (range) acyclovir AUC_{pl} of 29 900 (25 400–34 300) ng·L/h compares favorably to similar data from high-dose valacyclovir studies.^{14,15} In a dose-ranging study by Weller et al,¹⁴ the mean $\pm$ standard deviation acyclovir AUC was $21\,370 \pm 5310$ ng·L/h when valacyclovir 1500 mg was administered 4 times daily. In a randomized, double-blind, multicenter study of valacyclovir 1000 mg 3 times daily for 7 or 14 days versus acyclovir 800 mg 5 times daily for 7 days for the treatment of herpes zoster infection, Beutner et al¹⁵ estimated a mean daily acyclovir AUC after valacyclovir of 88 600 ng·L/h or 29 533 ng·L/h per dosing interval. Parameter estimates for CL/F and V/F were not reported in either study.

Acyclovir distribution in oral wash fluid-derived supernatant following valacyclovir has not been reported previously. This is important because evidence supports EBV production in salivary glands, oropharyngeal epithelial cells, and B cells in the oropharynx.^{16–20} Person-to-person transmission of EBV is believed to occur through exchange of infected oral fluids and cells. If EBV replication in the oral cavity is inhibited by antiviral therapy, then transmission of infectious virus may be reduced. We found that oral wash fluid-derived supernatant concentrations of acyclovir were 1.1% of the plasma concentrations following oral administration of valacyclovir. Van Dyke et al²¹ reported that acyclovir levels in saliva were 13% of plasma levels in adults who were taking oral acyclovir 200 mg every 4 hours, 5 times daily for herpes genitalis. This difference between studies could be attributable to the sample collection methods used. It is important to note that our method does not measure acyclovir concentrations directly in the saliva. Because it requires vigorous gargling of 20 mL of 0.9% normal saline for 30 seconds, the concentration of acyclovir in the final oral wash sample is diluted compared with direct salivary collection. Our oral wash method was used because it also collects oral epithelial cells that are necessary for qEBV analyses, and it was standardized to minimize intersubject variability in sample volume by using a fixed amount of normal saline rinse. Finally, neither our study nor the study by Van Dyke et al. found concentrations of acyclovir in saliva reflective of unbound concentrations in the plasma with unbound fractions reported to be 67 to 91%.⁹

The observed RUV_{pl} of 37% is somewhat higher than often observed in pharmacokinetic studies. This is perhaps elevated due to a changing physiological status secondary to the accompanying illness, or perhaps the virus itself is changing the pharmacokinetics over the time course of the concentration collection period. The RUV_{sup} of 51% is even higher. This can be due to all of the above reasons for a high RUV_{pl} but could also be a function of the oral wash methodology. There may be differences in subjects' thoroughness during the gargle and ability to produce saliva or in expectorating the full volume of the normal saline rinse.

We found that the half-life of EBV DNA decay during valacyclovir treatment was longest in the whole blood and shortest in the oral wash fluid-derived cell pellet. Viral rebound was also observed in the oral wash fluid-derived supernatant and cell pellet but not in the whole blood after completion of therapy. This suggests that the form of EBV DNA present in the oral cavity consists primarily of an actively replicating virus, which is most susceptible to an antiviral drug. The in vitro IC_{50} for acyclovir against EBV has been reported to be 0.3 μM or 67.5 ng/mL.¹¹ All acyclovir plasma concentrations measured in our study were well above this value. Four of 8 subjects had at least 1 acyclovir oral wash fluid-derived supernatant concentration above this value. Caution must be exercised when comparing in vitro concentrations to those measured in vivo because of known differences in protein binding. Although viral rebound was observed, by the end of the study 6 of the 7 subjects with primary EBV infectious mononucleosis still became asymptomatic (severity of illness score, 0). These findings are consistent with data from our earlier controlled trial of valacyclovir for primary EBV infectious mononucleosis.⁸

Acyclovir pharmacokinetic parameters and exposure metrics did not correlate with either virologic or clinical response metrics in this study. There are several possible reasons for no

detection of exposure-response relationships. It may have been due to our small sample size or that the standard valacyclovir dose administered produced a fairly limited range of acyclovir exposures. Alternatively, it is possible that the valacyclovir dose administered produced acyclovir exposures that were high on a maximum drug effect ($E_{\max}$) exposure-response curve where responses are maximized. In addition, the response metrics that we chose to examine may simply not be sensitive enough to detect relationships within the range of acyclovir exposures observed. Finally, acyclovir is not the active metabolite of valacyclovir. Acyclovir must first be taken up by virus-infected cells and phosphorylated to an active triphosphate metabolite that subsequently inhibits viral DNA synthesis. To date, intracellular acyclovir-triphosphate has not been measured in vivo. Future studies that determine the pharmacokinetics and pharmacodynamics of both acyclovir and acyclovir triphosphate are now needed. Although we did not find a pharmacokinetic-pharmacodynamic relationship, the quantity of EBV DNA decreased in all biologic matrices evaluated during the 7-day valacyclovir treatment period, which was likely due to a combination of the host's immune response and an antiviral drug effect. Finally, the investigational dose of valacyclovir used in this study was well tolerated and resulted in excellent adherence among study subjects.

CONCLUSIONS

Following administration of valacyclovir, acyclovir pharmacokinetics in young adults with EBV infectious mononucleosis were well described by a 1-compartment model. Acyclovir concentrations in oral wash fluid-derived supernatant were in rapid equilibration with those in plasma. Although concentrations of acyclovir in the oral wash fluid-derived supernatant were low compared with known unbound acyclovir concentrations in plasma, an anti-EBV effect in the oral cavity was observed. These data support the further study of valacyclovir for primary EBV infectious mononucleosis, including its ability to prevent person-to-person spread of this acute viral infection.

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Figure 1. Concentration-time curves for acyclovir in (a) plasma and (b) oral wash fluid-derived supernatant plotted on a semi-log scale following oral valacyclovir dosing.

Figure 2. Observed (OBS) versus model-predicted (PRED) acyclovir concentrations in (a) plasma and (b) oral wash fluid-derived supernatant following oral valacyclovir dosing in 8 subjects; solid line is the line of identity.

Figure 3. Median quantity of EBV DNA in oral wash fluid-derived supernatant, oral wash fluid-derived cell pellet, and whole blood in 7 subjects with primary EBV infectious mononucleosis treated with oral valacyclovir.

Figure 4. Median severity of illness scores in 7 subjects with primary EBV infectious mononucleosis treated with oral valacyclovir.

Table I**Baseline Subject Characteristics (N = 8)**

Characteristic	
Age, median (range), y	19.5 (18–20)
Sex ^a	
Male	4 (50)
Female	4 (50)
Race ^a	
White	8 (100)
EBV DNA, ^b median (range), copies/mL	
Whole blood	25 100 (1000–241 000)
Oral supernatant	11 650 (1000–110 500)
Oral cell pellet	58 400 (40–867 700)

^aData are number (%) of subjects.

^bCalculated as (day 0 or screening visit + day 1 or enrollment visit)/2.

Table II

Acyclovir Pharmacokinetic Parameters in 8 Subjects Following Oral Valacyclovir Dosing

Parameter	Estimate	Relative SE
CL/F, L/h	49.9	5.67%
V/F, L	74.1	22.5%
K _a	0.28	10.6%
F _{sup} , %	1.14	11.6%
Variability in CL/F, CV%	11.8	109%
Variability in V/F, CV%	20.0	196%
Variability in F _{sup} , CV%	15.5	110%
RUV _{pl} , CV%	36.9	29.6%
RUV _{sup} , CV%	50.8	21.3%

CL/F, apparent oral clearance; V/F, apparent volume of distribution; K_a, absorption rate constant; F_{sup}, fraction in oral wash fluid-derived supernatant; RUV_{pl}, residual unexplained variability in plasma; RUV_{sup}, residual unexplained variability in oral wash fluid-derived supernatant; CV, coefficient of variation for the between subject variability in the population; relative SE, measure of precision computed by dividing the standard error (SE) by the value of the estimate $\times 100$.