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Pharmacokinetics and Tolerance of Desciclovir, a Prodrug of Acyclovir, in Healthy Human Volunteers

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Because of the incomplete absorption of acyclovir (ACV) when given orally in humans, efforts have been made to develop a prodrug of ACV that would be better absorbed from the gastrointestinal tract and then converted in vivo to ACV. One such compound, desciclovir (DCV), is converted to acyclovir in vivo by xanthine oxidase. We gave each of 13 healthy volunteers 250 mg (about 3.25 mg/kg of body weight) of DCV orally thrice daily for 10 days, collected serial plasma and urine specimens, and measured DCV and ACV concentrations. The absorption of DCV was at least 75%, and almost two-thirds of the administered oral dose was recovered in the urine as ACV. Peak ACV levels in plasma were about 5 μg/ml and were reached in less than 1 h. The levels of ACV achieved in plasma were of the same magnitude as those reported for subjects given intravenous ACV at a dose of 2.5 mg/kg and approximately 10-fold higher than levels attained after administration of 200 mg of oral ACV every 4 h as measured in previous studies. The half-life of DCV was 0.85 ± 0.16 h, compared with 2.6 ± 0.5 h for ACV, indicating rapid conversion of DCV to ACV. There was no substantial increase in ACV levels in plasma on day 11 compared with day 2. No serious or consistent adverse effects were noted. In particular, the creatinine level in serum did not significantly rise in any subject and remained within the normal range in all.

Acyclovir (ACV) is effective in the treatment of infections caused by several members of the herpesvirus family, including herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus, and Epstein-Barr virus (1, 2, 6, 20, 31, 32). The gastrointestinal absorption of ACV is relatively poor, however, with a bioavailability of only about 20% (8, 23).

In an effort to achieve higher ACV levels in plasma, compounds that have minor alterations in the basic structure of ACV and that are converted in vivo to ACV have been developed. Some of these prodrugs appear to be better absorbed from the gastrointestinal tract than ACV and are then rapidly converted to ACV, leading to higher ACV levels in plasma than are attained by equivalent oral doses of ACV (15, 17). One such compound is 2-[(2-amino-9*H*-purin-9-yl)methoxy]ethanol, also known as 6-deoxyacyclovir, BW A515U, and desciclovir (DCV). This compound has no detectable activity against herpes simplex virus type 1 in vitro at 50 μg/ml (17), but is converted to ACV by xanthine oxidase (14, 17). Previous studies have shown good absorption and rapid conversion to ACV when this compound was given in single doses or short multiple-dose courses to immunocompromised patients (29), but its pharmacokinetics and tolerance in healthy subjects during a more conventional treatment period have not been assessed previously. This study was designed to evaluate the safety and pharmacokinetics of DCV given at a dose of 250 mg every 8 h for 10 days to healthy young adult subjects.

MATERIALS AND METHODS

Thirteen subjects with a history of past herpesvirus infections were entered into the study. Written informed consent was obtained from all subjects. There were 11 men and 2 women, of ages 19 to 49 years. None of the subjects had an estimated creatinine clearance less than 50 ml/min as determined by Kampmann nomogram (13), hepatic dysfunction, gastrointestinal dysfunction, or any other identifiable clinically significant abnormality. None of the subjects received antiviral chemotherapy or xanthine oxidase inhibitors during the study or within 1 week of entering the study. The seven subjects at The Johns Hopkins University were housed for the project at quarters near the hospital, while the six subjects at The University of Alabama were outpatients, except for the days when blood samples for kinetic studies were obtained, when they were admitted to the Clinical Research Unit of The University of Alabama hospital.

The subjects received 31 doses of 250 mg of DCV every 8 h (10.33 days). The doses were administered at least 1 h before meals, except on days 2, 5, and 11, when the morning dose was given after an overnight fast and was followed by an additional 4-h fast, except for water. It was on these days (kinetics days) that the samples for the kinetic studies were collected. Blood samples were obtained at 0.0, 0.5, 1, 2, 4, 6, 8, 12, and 18 h after the morning dose. The subjects started 24-h urine collections just before the morning dose of DCV was administered on the kinetics days, except for day 11, when the 24-h urine collection was begun on day 10. The blood samples and urine collections were stored frozen at −20°C for subsequent analysis of both DCV and ACV levels. Precautions to prevent in vitro conversion of DCV to ACV in human blood are not necessary (H. C. Krasny, unpublished data). The ACV concentrations in plasma and urine were measured by radioimmunoassay specific for ACV (24), and the DCV concentrations were measured in a similar fashion by an assay specific for DCV (25). The lower limits of detectability were 2 ng/ml for ACV and 1 ng/ml for DCV, and the coefficient of variation was within 10%.

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TABLE 1. Pharmacokinetic parameters[a]

Study day	ACV						DCV
	AUC_{0-8} (h · μg/ml)	C_{max} (μg/ml)	T_{max} (h)	C_{min} (μg/ml)	CL/F (ml/min per 1.73 m^2)	CL_R (ml/min per 1.73 m^2)	AUC_{0-8} (h · μg/ml)
2	11.8 ± 2.0	4.55 ± 1.01	0.93 ± 0.40	0.30 ± 0.10	347 ± 68	207 ± 82	1.78 ± 0.92
5	11.1 ± 2.4	5.07 ± 1.76	0.80 ± 0.26	0.26 ± 0.12	363 ± 70	234 ± 52	1.95 ± 0.99
11	12.4 ± 2.7	5.57 ± 1.63	1.08 ± 0.95	0.25 ± 0.08	335 ± 76	252 ± 38	2.58 ± 1.87
P^b	0.41	0.26	0.53	0.53	0.62	0.37	0.31

The subjects were monitored for symptomatic adverse experiences by nondirective inquiry. Clinical laboratory tests to monitor for changes in serum chemistries, hematology, and urinalysis were performed before the initiation of drug therapy, midway through the course of therapy, and at the completion of treatment. These tests included serum electrolytes, urea nitrogen, creatinine, glucose, transaminases, total protein, albumin, calcium, phosphate, uric acid, cholesterol, alkaline phosphatase, complete blood count, and dipstick and microscopic urine examination.

Plasma concentration-time data for DCV and ACV were subjected to model-independent and model-dependent analyses. For model-independent analysis, the observed peak concentrations in plasma (C_{max}), the time to peak (T_{max}), the trough concentration (C_{min}), and the area under the plasma concentration-time curves for the 8-h dosing interval (AUC_{0-8}) were determined after the first dose on days 2, 5, and 11. The AUC_{0-8} of ACV was determined by the linear trapezoidal rule (33). When the gaps of sampling time were greater than twice the terminal half-life of the drug, AUC values determined by the linear trapezoidal rule would be substantially overestimated (33). The AUC_{0-8} of DCV was determined by the log-linear trapezoidal rule (33). These model-independent parameters were measured at steady state.

Model-dependent analysis was used mainly to determine the terminal half-lives of ACV and DCV. Visual inspection of a semilogarithmic plot of the ACV concentration-time curve revealed a biexponential decline after the peak. ACV data were best fitted by a two-compartment open model with first-order input. The DCV concentration-time curve revealed a monoexponential decline after reaching the peak. DCV data were best fitted by a one-compartment open model with first-order input. The NONLIN nonlinear regression program (22) was used to fit the models to the data. A weighting function of reciprocal drug concentration was used in the NONLIN analysis because it could better approximate the reciprocal variance of repeated assays of both drugs. The CSTRIP computer program (28) was used to obtain initial estimates. The model-dependent pharmacokinetic parameters were calculated by using equations as described by Gibaldi and Perrier (12). The apparent total body clearance was calculated from the equation CL/F = Dose/AUC, where Dose is the amount of DCV administered and AUC is the area under the concentration-time curve at steady state for multiple dosing. Renal clearance was calculated from the equation $CL_R = A_e/AUC$, where A_e is the amount of drug excreted in the urine and AUC is the area under the concentration-time curve over the same time interval as the urine collection.

The model-independent pharmacokinetic parameters, AUC, C_{max}, T_{max}, CL/F, and CL_R of both ACV and DCV on different study days were compared by Duncan's multiple range test. The Statistical Analysis System General Linear Models (GLM) procedure was applied to this test. Also, the urinary recovery data and the model-dependent half-life of DCV on different study days were compared by the same test.

RESULTS

The subjects ranged in age from 19 to 49 years (mean, 31 years). The mean height (± standard deviation) was 176 ± 9 cm, the mean weight was 79 ± 10 kg, and the mean body surface area was 1.98 ± 0.16 m^2. Each subject received 250 mg of DCV every 8 h. The dose per kilogram of body weight was 3.22 ± 0.43 mg.

The model-independent pharmacokinetic data for study days 2, 5, and 11 are summarized in Table 1, and the mean concentration-time curves for ACV and DCV are shown in Fig. 1. Peak ACV levels in plasma (C_{max}) were reached within 1 h. The C_{max} remained fairly consistent throughout the study. No significant differences ($P > 0.05$) were found in AUC_{0-8} or C_{max} between different study days by Duncan's multiple range test. The peak ratio of ACV to DCV in plasma was approximately 4:1. The mean ACV concentration in plasma was ≥2 μg/ml for 2 h after dosing and fell to 0.5 μg/ml at 6 h after dosing. The mean recovery of ACV plus DCV in urine was 65 to 75% of the administered dose, with a tendency for slightly increased recovery in urine after longer periods of drug administration, but this difference did not reach statistical significance by analysis of variance testing. The ratio of excretion of ACV to DCV in urine was approximately 10:1.

As indicated earlier, model-dependent pharmacokinetic analysis was applied mainly to determine the terminal half-lives of DCV and ACV. The ACV data over the 8-h periods on study days 2 and 5 were not analyzed by the model-dependent method, because limited time points in the terminal phase did not allow meaningful half-life determinations. The ACV data obtained over a 24-h period after the last dose of DCV on day 11 were best fitted by a two-compartment model with first-order input. The model-dependent pharmacokinetic parameters of DCV on study days 2, 5, and 11 were determined separately. The DCV data were best fitted by a one-compartment model with first-order input. The model-dependent pharmacokinetic parameters are summarized in Table 2. The half-life of DCV was about 50 min, while the half-life of ACV was 2.6 ± 0.5 h. There was only modest interindividual variability in the observed pharmacokinetic parameter values.

Only four subjects reported any symptoms following the initiation of the medication. All four complained of lethargy,

TABLE 1—*Continued*

DCV					Recovery in urine (% of dose)		
C_{max} (μg/ml)	T_{max} (h)	C_{min} (μg/ml)	CL/F (ml/min per 1.73 m^2)	CL_R (ml/min per 1.73 m^2)	ACV	DCV	Total
1.23 ± 0.58	0.77 ± 0.26	0.01 ± 0.02	2,555 ± 1,167	148 ± 117	59.1 ± 16.1	5.8 ± 3.7	64.9 ± 18.2
1.50 ± 0.67	0.75 ± 0.27	0.004 ± 0.006	2,240 ± 879	132 ± 52	65.4 ± 13.2	6.5 ± 3.1	71.8 ± 13.3
1.58 ± 0.93	0.67 ± 0.25	0.01 ± 0.02	1,968 ± 991	126 ± 53	67.8 ± 18.4	7.2 ± 4.8	74.9 ± 19.8
0.46	0.56	0.66	0.28	0.80	0.40	0.69	0.36

[a] All values are presented as mean ± standard deviation.
[b] Comparison was made of low through high mean values by using Duncan's multiple range test. Table shows *P* values associated with this comparison.

two complained of indigestion, two complained of increased appetite, one complained of increased energy, and one complained of vivid dreams. One subject developed nausea and vomiting after the first dose but without recurrence, even though the drug administration was continued. All of the subjective effects reported were in volunteers at Johns Hopkins, who were housed in a modestly restrictive environment near the hospital, whereas none of the volunteers participating primarily as outpatients at Alabama complained of any adverse effects. Furthermore, none of these symptoms was serious enough to suggest that the experiment should be stopped prematurely, and most symptoms resolved spontaneously despite continuation of the medication. One subject withdrew from the experiment on day 5 because of personal reasons and not for any adverse effect.

No laboratory tests consistently changed over the course of therapy. The absolute eosinophil count for one subject increased from 480 to 737/mm^3 over the treatment course. Two subjects had transient and minimal increases in alanine aminotransferase levels in serum during treatment to levels just over the upper limit of normal, but the levels were normal when checked 8 days after treatment. Neither of these changes was thought to be clinically significant, nor were they associated with any other evidence of hypersensitivity or hepatic dysfunction. There was no significant increase ($P > 0.05$) in creatinine or urea nitrogen in serum over the course of the study by analysis of variance, and neither of these measures of renal function rose beyond the normal range.

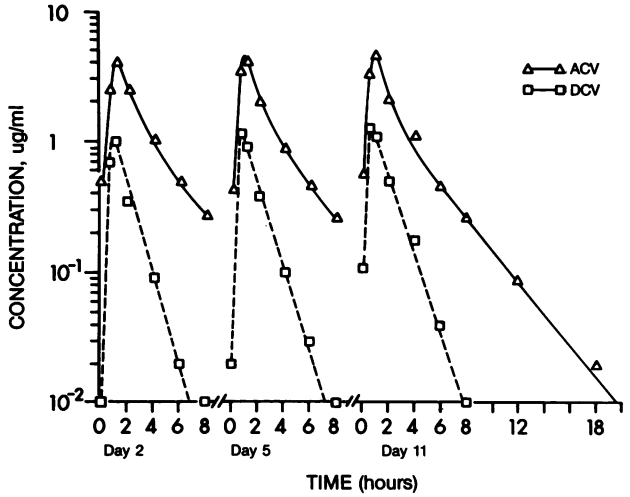

FIG. 1. Mean concentrations of ACV and DCV in plasma after multiple dosing with 250 mg of DCV every 8 h for 10 days and one additional dose on day 11.

DISCUSSION

The development of ACV has provided a potent agent in the therapy of infections caused by viruses in the herpesvirus family. Of the members of this family, the most sensitive to ACV is herpes simplex virus. Varicella-zoster virus and Epstein-Barr virus are somewhat less sensitive, and cytomegalovirus is relatively resistant (11). The ACV level required to inhibit the replication of these viruses by 50% (ED_{50}) is as follows (in micrograms per milliliter): herpes simplex virus type 1, 0.01 to 0.45; herpes simplex virus type 2, 0.01 to 0.72; varicella-zoster virus, 0.36 to 1.1; Epstein-Barr virus, 0.07 to 1.6; and cytomegalovirus, 2.25 to >22 (7, 21). The clinical effectiveness of parenteral ACV is well documented for herpes simplex virus infections (20, 26, 31), including encephalitis (30, 32), and for varicella-zoster virus infections (2, 3). Obviously, the use of parenteral therapy is impractical for patients who are not seriously ill or immunosuppressed. Oral ACV has been developed as a potential alternative for patients who do not require hospitalization. Although oral ACV has limited absorption and leads to relatively low levels in plasma (8), these levels are adequate to allow successful treatment of primary herpes simplex virus infections (6) and reduce the recurrence of genital herpes when given in low doses as a prophylactic measure (10). Use of oral ACV in treatment of Epstein-Barr virus, a less susceptible member of the herpesvirus family, has been inconclusive, perhaps owing to the modest absorption of ACV and hence to the short duration of ACV levels exceeding the ED_{50} for the organism (34). Levels in plasma following administration of oral ACV, even after oral doses of 1,000 mg every 4 h, usually reach only 2 to 3 μg/ml (P. de Miranda, S. Liao, D. A. Page, and M. R. Blum, unpublished data). Thus, the practical limitations of parenteral ACV treatment and the modest gastrointestinal absorption of oral ACV have stimulated interest in finding an alternative oral compound such as DCV with better absorption properties and prompt conversion to ACV.

This study shows that DCV is a prodrug that can be given at a dose of 250 mg every 8 h for 10 days with excellent ACV levels in plasma and good clinical tolerance. The peak levels of ACV in plasma exceeded by nearly 10-fold those which would be expected from 200-mg doses of oral ACV every 4 h, and the areas under the concentration-time curves of ACV were nearly 8-fold greater, based on previous studies (8). Furthermore, the ACV levels achieved in this project exceeded the in vitro ED_{50} for varicella-zoster virus and Epstein-Barr virus for 2 to 6 h (see above). Giving an

TABLE 2. Model-dependent pharmacokinetic parameters of ACV and DCV after oral administration of 250 mg of DCV every 8 h[a,b]

Drug and time of administration	$AUC_{0-\infty}$ (h · μg/ml)	CL/F (ml/min per 1.73 m^2)	$t_{1/2\beta}$ (h)	V_1/F (liter/kg)	V_β/F (liter/kg)	V_{ss}/F (liter/kg)
ACV						
Day 11	11.9 ± 2.9	351 ± 90	2.6 ± 0.5	0.34 ± 0.17	1.17 ± 0.49	0.73 ± 0.27
DCV						
Day 2	1.77 ± 1.02	2,642 ± 1,258	0.84 ± 0.16	2.80 ± 1.74		
Day 5	1.84 ± 1.06	2,576 ± 1,298	0.84 ± 0.15	2.67 ± 0.82		
Day 11	2.64 ± 1.98	1,995 ± 1,081	0.87 ± 0.19	1.99 ± 0.82		
Overall	2.08 ± 1.44	2,405 ± 1,216	0.85 ± 0.16	2.49 ± 1.40		

[a] ACV data were best fitted by a two-compartment model with first-order input, and DCV data were best fitted by a one-compartment model with first-order input.

[b] Definitions of model-dependent pharmacokinetic parameters: $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; CL/F, apparent total body clearance after oral dosing, where F is the extent of bioavailability; $t_{1/2\beta}$, half-life of the terminal exponential phase in the concentration-time curve; V_1, volume of distribution of the central compartment; V_β, CL/β, where β is the rate constant of the terminal phase; V_{ss}, steady-state volume of distribution.

increased dose of DCV at the same interval might well be expected to provide ACV levels in plasma that remained above the ED_{50} for varicella-zoster virus and Epstein-Barr virus for even longer periods.

The peak levels seen in this study are similar to those reported in previous studies of similar doses of DCV. In a study in which the drug was given every 6 h to patients with hematological malignancies (29), the peak ACV levels in plasma were nearly fourfold higher than the peak DCV levels in plasma, and both peaks occurred within 1 h of drug administration.

The 24-h recovery of ACV plus DCV in urine in this study (65 to 75% of the administered oral dose) was nearly equivalent to the amount of ACV recovered in urine after administration of ACV intravenously (9), indicating that DCV was almost completely absorbed. The majority of DCV was rapidly converted to ACV (Table 2). Further metabolism to the carboxyl metabolites of ACV and DCV has been detected in the urine of a selected group of these subjects (16) and is comparable to the amount of carboxyl metabolite found in urine after intravenous ACV administration (9).

Renal impairment, as defined by an increase in urea nitrogen and/or creatinine levels in serum, has been observed in patients treated with intravenous ACV. This appears to occur predominantly when the intravenous ACV is given rapidly (5). Double-blind placebo-controlled studies have generally shown that when ACV is infused slowly, i.e., over 50 to 90 min, renal impairment in excess of that observed in the placebo groups does not occur (2, 26, 31), although in one outpatient study, the higher dose used to treat herpes zoster virus (500 mg/m^2 thrice daily) was associated with renal impairment (3). Animal studies indicate that the renal toxicity observed with rapid intravenous administration is associated with crystal formation in renal tubules (5). In contrast to intravenous ACV, oral ACV is more slowly and poorly absorbed (8), and significant renal toxicity was not a feature of clinical trials in which patients received up to 1,000 mg of oral ACV per day (10). Despite the rapid absorption of DCV and rapid conversion to ACV noted in our volunteers, no renal toxicity was encountered.

The enzyme xanthine oxidase, which is instrumental in the conversion of DCV to ACV, is present in various tissues in the body, but the greatest concentrations are in the liver and intestines (18). Enzymatic conversion during the first pass through either or both of these organs could account for the rapid conversion of DCV to ACV after absorption.

Data on ACV levels in plasma following an oral dose of 200 mg of ACV were best fitted to a one-compartment model, unlike the ACV data following a 1-h intravenous infusion, which were best fitted to a two-compartment model (8). This was due to a comparatively slow absorption phase, which obscured the rapid distribution phase of ACV. However, after oral dosing of DCV there was rapid absorption and extensive presystemic conversion to ACV. Therefore, the ACV data revealed a biphasic decay after the peak. The terminal half-life of ACV after oral dosing of DCV was 2.6 h, which is similar to the terminal half-life of ACV after intravenous and oral dosing of ACV.

The apparent clearances CL/F of ACV and DCV were 351 ± 90 and 2,405 ± 1,216 ml/min per 1.73 m^2, respectively (Table 2). The F terms in the denominator of CL/F for ACV and DCV actually represent two different parameters. The F term for ACV represents the fraction of dose converted to ACV presystemically and systemically after oral dosing of DCV, which approaches 1, based on the urinary recovery data. The CL/F of ACV is quite comparable to the total body clearance of ACV after intravenous infusion of ACV in patients with normal renal function (327 ± 80 ml/min per 1.73 m^2) (4), which also indicates extensive conversion of DCV to ACV. The large mean value of CL/F of DCV and large intersubject variability associated with the CL/F (coefficient of variation, 50%) indicate extensive first-pass conversion of DCV. The F term for DCV represents the extent of bioavailability of DCV, which is presumably a very small fraction of the dose (possibly around 0.1) owing to the extensive first-pass conversion to ACV.

It appears that DCV is a prodrug of ACV that is capable of circumventing the low oral bioavailability of ACV and one that is well tolerated. The ACV levels achieved after administration of 250 mg of DCV were comparable to those observed in subjects given ACV at 2.5 mg/kg intravenously (19) and to the simulated plasma concentration-time curve of ACV after multiple 1-h intravenous infusions of 2.5 mg of ACV per kg of body weight every 8 h (Fig. 2), based on the pharmacokinetic parameters of patients with normal renal function (4). No substantial accumulation of ACV or DCV occurred over 10 days of treatment, and therapy was tolerated well. This compound may allow oral therapy in settings in which only intravenous ACV therapy was previously thought to be useful. It may also improve upon the efficacy seen with oral ACV therapy. Although the clinical experience with DCV is very limited and conclusions must be drawn cautiously at this point, a recent report describes the use of DCV with apparent clinical response in a patient with

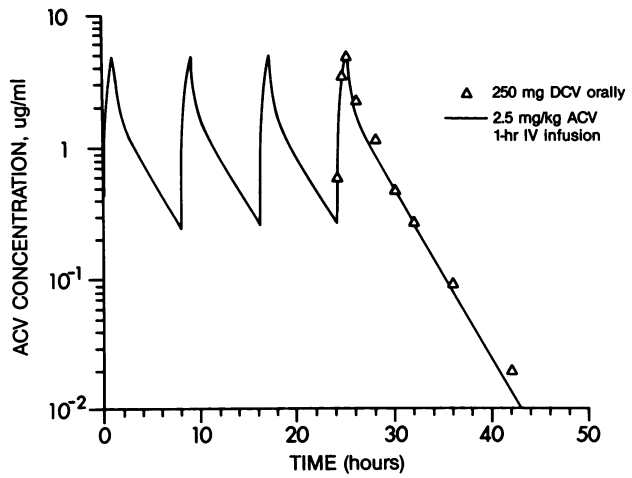

FIG. 2. Comparison of mean ACV concentrations in plasma (on day 11) after multiple oral dosing of 250 mg of DCV every 8 h with simulated concentrations in plasma after multiple 1-h intravenous (IV) infusions of 2.5 mg of ACV per kg of body weight every 8 h.

chronic Epstein-Barr virus infection, with peak ACV levels in plasma similar to those achieved in our subjects (27).

Thus, DCV may answer the need for an agent that, administered orally, will provide ACV levels similar to those achieved by parenteral therapy. Not only would DCV therapy allow for outpatient oral treatment in cases in which parenteral therapy is now required, but it also would result in higher ACV levels after dosage with a single 250-mg DCV capsule than are currently achieved after dosage with five 200-mg ACV capsules.

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