Single-Dose Pharmacokinetics of Acyclovir

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The pharmacokinetics of intravenously administered acyclovir were studied in 10 patients with advanced malignancies. After doses of 0.5 and 1.0 mg/kg, the slow disposition half-life values ($t_{1/2\beta}$) ranged from 2.2 to 3.1 h for the 1-h infusions and from 1.8 to 3.7 h for the 6-h infusions. Plasma levels, measured by radioimmunoassay, reached a maximum at the end of the 1-h infusions and approached steady state at 3 to 4 h into the 6-h infusions. Mean peak plasma concentrations obtained at 0.5 and 1.0 mg/kg administered over 1 h were 3.03 and 5.99 μM, respectively. Mean peak levels for the 6-h infusions were 1.07 μM at 0.5 mg/kg and 2.58 μM at 1.0 mg/kg. The mean urinary elimination of acyclovir was 44.7% of the administered doses. No clinical or laboratory abnormalities were noted in the 10 patients studied.

Acyclovir (ACV), 9-(2-hydroxyethoxy-methyl)guanine, is a new antiviral agent that has been shown in vitro as well as in animal models to be effective against certain herpesvirus infections (2, 4, 5, 9, 11, 13). The pharmacokinetics of ACV have been previously reported after 1-h infusions in man (3). This study examines single-dose pharmacokinetics and tolerance of ACV in humans after 1- and 6-h infusions at two dose levels.

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MATERIALS AND METHODS

Patients. The seven men and three women who participated in this study were all adults with advanced malignancies at risk of developing progressive herpes group viral infections. The patients ranged from 37 to 78 years of age, with a mean of 60.5 (±15.3, standard deviation [SD]) years. Their weights ranged from 51 to 93 kg with a mean of 70.3 (±15.8, SD) kg. Informed consent was obtained from each subject. Patients were excluded from the study if they had received any anticancer or antiviral chemotherapy within 1 week of enrollment in the study, were women of child-bearing potential, or had evidence of hepatic or renal dysfunction.

Drug administration and sample collection. The lyophilized sodium salt of ACV (prepared by Wellcome Research Laboratories) was dissolved in sterile water for injection to a final concentration of 20 mg/ml. The dosage of ACV to be administered was then diluted to a total volume of 52 or 58 ml with lactated Ringer's solution for the 1- and 6-h infusions,

respectively. The drug was administered intravenously by a constant rate infusion pump over the appropriate period at dosages of 0.5 or 1.0 mg/kg. Heparinized venous blood samples were obtained from the arm contralateral to that used for ACV infusion. For the 1-h infusion, samples were collected before administration of ACV, at 0.17, 0.33, 0.50, and 1.0 h into the infusion, and then at 0.17, 0.33, 0.5, 1, 2, 4, 6, 10, 18, and 36 h postinfusion. For the 6-h infusion studies, blood specimens were drawn before initiation of the infusion, at 1, 2, 3, 4, 5, and 6 h during infusion, and at 0.17, 0.33, 0.5, 1, 2, 4, 6, 12, 18, and 36 h postinfusion. Blood samples were immediately centrifuged. The separated plasma was frozen for subsequent analysis. All urine was collected at the following periods: 0 to 1, 1 to 5, 5 to 9, 9 to 13, 13 to 25, 25 to 48, and 48 to 72 h for the 1-h infusion; and 0 to 6, 6 to 10, 10 to 14, 14 to 24, 24 to 48, and 48 to 72 h for the 6-h infusion. We have found that freeze-thawing of samples over at least a 2-year period has no noticeable effect on radioimmunoassay-identifiable ACV (unpublished data).

Toxicity surveillance. Patients were evaluated for renal, hepatic, and hematological function before dosing and at 3 days and 1, 2, and 3 weeks postinfusion. These studies included a complete and differential blood count, reticulocyte and platelet counts, analysis of serum for glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, creatinine, urea nitrogen, alkaline phosphatase, total bilirubin, uric acid, and glucose levels, and urinalyses. Patients were assessed for symptoms of drug toxicity daily for the initial 3 days postinfusion and then weekly for the next 3 weeks.

Radioimmunoassay for ACV. Plasma and urine concentrations of ACV were determined by the radioimmunoassay procedure developed by Quinn et al. (12) and field tested and validated by Hintz et al. (6). The assay has been shown to be highly specific for ACV and is capable of detecting 100 pmol of the drug

per ml (6, 12). All assays were run in triplicate. The standard curve data were subjected to computer analysis, using an iterative weighted least-squares regression analysis, and the unknowns were determined from the regression equation.

Pharmacokinetic analysis. Initial inspection of the postinfusion plasma concentrations of ACV versus time revealed that ACV exhibited a biexponential decline. The pharmacokinetics of ACV were analyzed, therefore, by using the nonlinear least-squares regression program, NONLIN (10), with a specific subroutine for a two-compartment pharmacokinetic model

with zero-order input (10). The plasma concentration of drug (C_1) was described by the equation

$$C_1 = \frac{k_0(k_{21} - \alpha)(1 - e^{\alpha T})e^{-\alpha \tau}}{V_1\alpha(\alpha - \beta)}$$

$$+ \frac{k_0(k_{21} - \beta)(1 - e^{\beta T})e^{-\beta \tau}}{V_1\beta(\beta - \alpha)}$$

where k_0 is the rate of infusion, k_{21} is the distribution rate constant out of the peripheral compartment, α and β are the rapid and slow disposition rate constants,
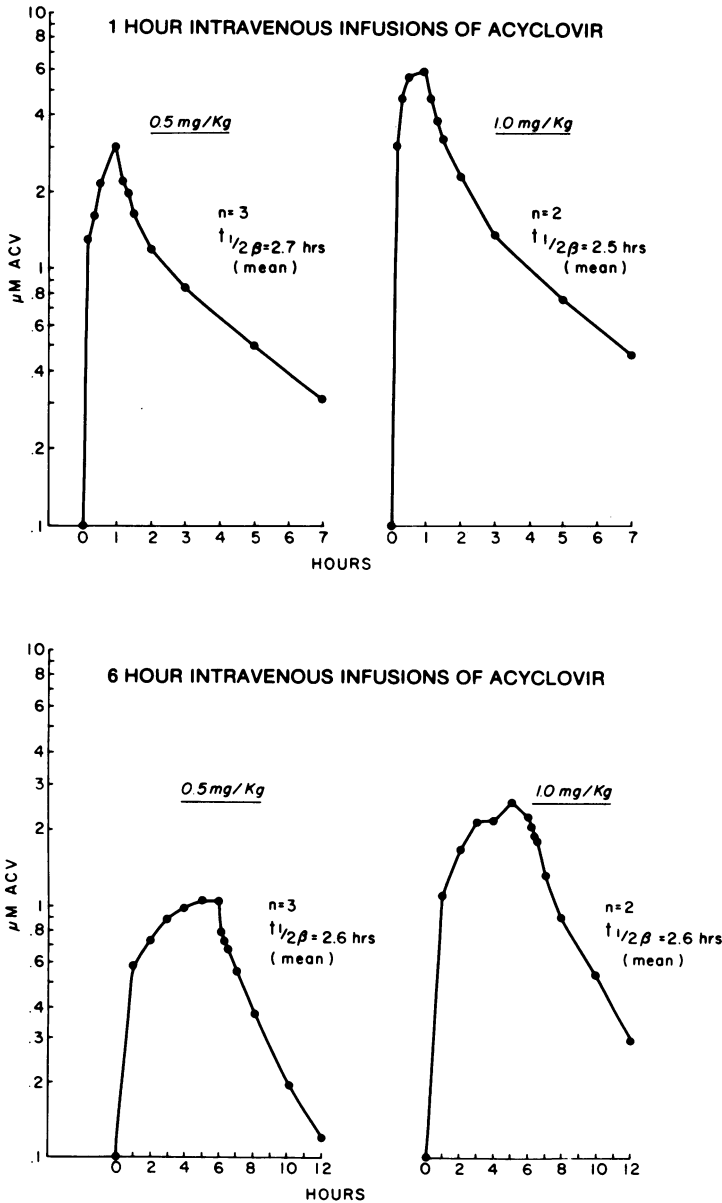

FIG. 1. *Mean plasma levels of ACV after 1- and 6-h intravenous infusions.*

respectively, V_1 is the apparent volume of distribution of the central compartment, T is the duration of infusion at time τ, and τ is the time from the beginning of the infusion. Best fit estimates were used for V_1, k_{10}, k_{12}, and k_{21}. Additionally, the volume of distribution at steady state (Vd_{ss}) and the total body clearance (TBC) were defined by the following equations:

$$Vd_{ss} = \frac{V_1(k_{12} + k_{21})}{k_{21}} \text{ and } TBC = \frac{dose}{AUC_0^\infty}$$

where k_{12} is the distribution rate constant into the peripheral compartment and AUC_0^∞ represents the area under the plasma concentration time curve calculated from 0 to infinity via the trapezoidal rule. The slow disposition plasma half-life ($t_{1/2\beta}$) was determined by the equation $t_{1/2\beta} = \ln2/\beta$.

RESULTS

The highest plasma levels of ACV were obtained at the end of the 1-h intravenous infusions. During the 6-h infusions, plasma levels approached steady state at 3 to 4 h into the administration. Mean peak plasma concentrations for 0.5- and 1.0-mg/kg 1-h infusions were 3.03 and 5.99 μM, respectively (Fig. 1). Peak mean plasma levels during the 6-h infusions were 1.07 μM after a dose of 0.5 mg/kg and 2.58 after a dose of 1.0 mg/kg (Fig. 1). Postinfusion plasma levels of ACV exhibited a biphasic decline. The data was well fitted to a two-compartment model with zero-order input, as indicated by small and randomly distributed percent deviations calculated from observed concentrations approaching 1.0. The pharmacokinetic parameter values for each patient are presented in Table 1. The mean slow disposition half-life values ($t_{1/2\beta}$) for the 1-h infusions were 2.7 and 2.5 h for the 0.5 and 1.0 mg/kg dosages; for the 6-h infusions, the mean $t_{1/2\beta}$ was 2.6 h for both dosages. The $t_{1/2\beta}$ for the 10 patients studied ranged from 1.8 to 3.7 h. The mean V_1 and Vd_{ss} were 0.362 (±0.162, SD) and 0.792 (±0.176, SD) liters/kg of body weight, respectively. The total body clearance for patients studied ranged from 3.84 to 4.88 ml/min per kg and did not substantially change with the two doses or dosage schedules.

The percent urinary recovery of radioimmunoassay-identifiable (essentially unmetabolized) ACV administered to the patients studied ranged from 32.7 to 57.5%, with a mean of 44.7% (±8.3, SD). Urinary elimination of ACV occurred rapidly, with a mean of ∿60% of the recovered drug excreted by 6 h and over 99% of the recovered ACV detected in the urine within 24 h postinfusion (Fig. 2).

No adverse reactions were observed at the intravenous sites during or after the intravenous infusion of ACV. Similarly, no clinical or labo-

TABLE 1. Two-compartment open model pharmacokinetic parameter values for ACV after intravenous infusion of 0.5 or 1.0 mg/kg[a]

Patient no.	Infusion time (h)	Dose (mg/kg)	α (h^{-1})	β (h^{-1})	$t_{1/2\beta}$ (h)	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	V_1 (liter/kg)	Vd_{ss} (liter/kg)	AUC (nmol/h per ml)	Serum creatinine (mg/dl)	Creatinine clearance (ml/min per 1.73 m^2)	Urinary recovery (%)	TBC (ml/min per kg)	r
1	1	0.5	2.1	0.22	3.1	0.83	1.0	0.45	0.66	1.2	7.58	0.8	93	54.8	4.88	0.998
2	1	0.5	1.4	0.25	2.8	0.49	0.63	0.58	0.48	0.86	8.24	1.2	99	34.1	4.49	0.969
3	1	0.5	4.7	0.32	2.2	2.5	1.0	1.4	0.18	0.61	8.65	0.9	60	47.8	4.28	0.989
4	1	1.0	2.9	0.28	2.5	1.4	0.77	1.0	0.29	0.81	15.2	1.2	79	50.0	4.86	0.988
5	1	1.0	2.7	0.28	2.5	1.2	0.68	1.1	0.26	0.72	15.7	1.0	71	47.4	4.70	0.968
6	6	0.5	4.2	0.39	1.8	2.0	1.0	1.6	0.22	0.64	6.18	0.9	73	57.5	6.00	0.998
7	6	0.5	0.96	0.19	3.7	0.3	0.4	0.45	0.54	0.95	9.63	1.0	80	43.3	3.84	0.884
8	6	0.5	5.0	0.32	2.2	2.8	1.1	1.5	0.20	0.69	7.82	0.9	68	41.2	4.73	0.987
9	6	1.0	1.5	0.26	2.7	0.51	0.62	0.62	0.44	0.80	17.0	1.0	59	38.4	4.37	0.976
10	6	1.0	1.6	0.29	2.4	0.49	0.58	0.77	0.35	0.65	17.2	0.7	66	32.7	4.43	0.995
Mean			2.7	0.28	2.6	1.25	0.78	0.95	0.36	0.80				44.7	4.66	
SD			±1.5	±0.06	±0.53	±0.90	±0.23	±0.43	±0.16	±0.18				±8.3	±0.57	

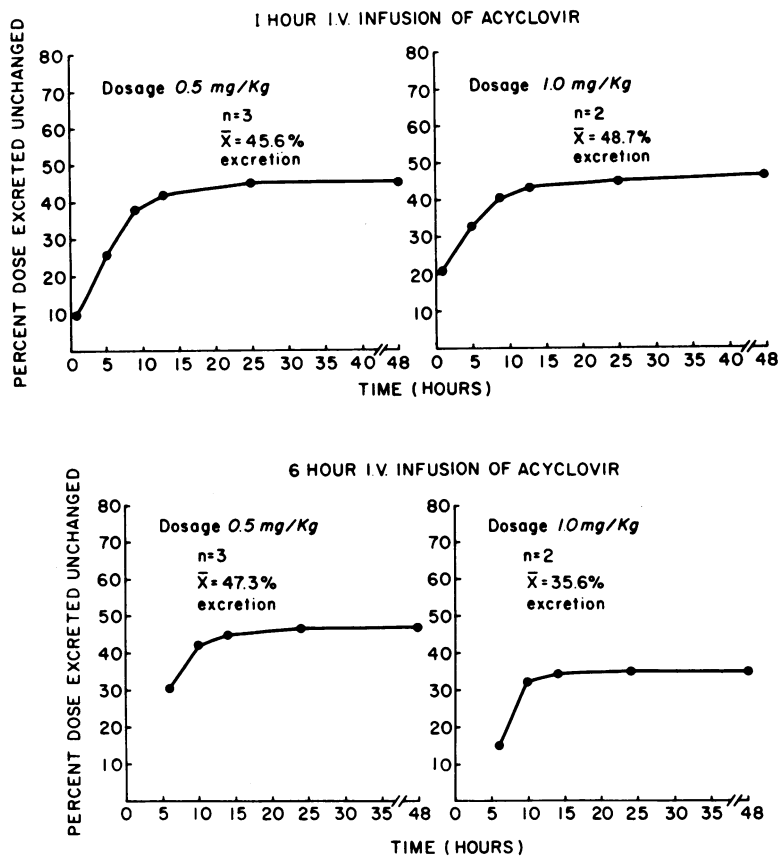[a] AUC, Area under the curve; TBC, total body clearance.

FIG. 2. *Cumulative percent urinary recovery of ACV after 1- and 6-h intravenous (I.V.) infusions.*

ratory signs of systemic toxicity were detected during the 3-week follow-up period.

DISCUSSION

This single-dose pharmacokinetic study of ACV indicates that the drug is capable of achieving predictable peak plasma levels at doses of 0.5 and 1.0 mg/kg during 1- and 6-h infusions. At 1.0 mg of ACV per kg administered over 1 h, the mean peak plasma levels achieved are 40 times the 50% inhibitory dose published by Crumpacker et al. (2) for HSV-1 (0.15 μM), 4 times that for HSV-2 (1.62 μM), and 1.5 times that for VZ (3.75 μM). After discontinuation of ACV, there was a biexponential decline in the detectable plasma levels. The mean $t_{1/2\beta}$ for the 10 patients studied was 2.58 ($\pm$0.54, SD) h. In other rising-dose studies, de Miranda et al. (3) reported plasma peak ACV concentrations of 33 μM when 5 mg/kg was administered over 1 h. Their findings are consistent with this study and suggest that plasma levels achievable with ACV are directly proportional to the dose administered.

The urinary recovery of unmetabolized ACV as measured by radioimmunoassay for the patients examined ranged from 32.7 to 57.5% of the total dosage administered. The fate of the ACV not recovered in our patients is presently unclear. Animal studies suggest that a small portion of ACV is metabolized to 9-carboxymethoxymethylguanine and 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine (3). De Miranda et al. recently found, by high-performance liquid chromatography, that a metabolite (probably 9-carboxymethoxymethylguanine) could be found in the urine of individuals given ACV (3). This metabolite composed 2 to 14% of the dose administered to their patients. It is currently unclear as to whether there are other metabolites. In addition, it is possible that ACV is cleaved to guanine and, after deamination to xanthine, enters the uric acid pool. Currently, patients are being given radiolabeled ACV to clarify the metabolic fate of ACV in humans.

This study indicates that ACV in low doses is well tolerated by patients and possesses properties which give it several advantages over cur-

rently available anti-herpes antimicrobial agents. Adenine arabinoside (9-β-arabinofuranosyl-adenine; Ara-A) has recently been approved for the treatment of herpes simplex encephalitis and may be useful for other herpesvirus infections. Ara-A, however, has a low therapeutic index, being rapidly deaminated in humans to arabinosylhypoxanthine, which has an antiviral activity much lower than that of the parent compound (1, 14). In addition, Ara-A is relatively insoluble and requires large volumes of intravenous fluids for administration (7, 8). The substantially greater solubility of ACV combined with its high therapeutic index and low toxicity offers potentially important advantages over Ara-A. The pharmacokinetic properties of ACV described in this study suggest that continuous intravenous infusions may not be necessary and that multiple dosage schedules may be useful therapeutically. Studies are in progress to evaluate the clinical efficacy of ACV in human herpesvirus infections.

ACKNOWLEDGMENTS

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