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Pharmacokinetics of Foscarnet after Twice-Daily Administrations for Treatment of Cytomegalovirus Disease in AIDS Patients

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The pharmacokinetics of foscarnet were evaluated in 11 AIDS patients with cytomegalovirus disease after twice-daily infusion of 90 mg/kg of body weight for 2 weeks. All patients were hydrated during foscarnet infusion. Blood and urine samples were collected on days 1, 7, and 14 of therapy. Foscarnet concentrations were measured by high-pressure liquid chromatography. Despite large interindividual variations, no significant differences were seen between day 1, day 7, and day 14 concentrations in plasma. Mean peak and trough concentrations on day 14 of therapy were 605 ± 118 and 52 ± 59 μM, respectively. In all patients, peak concentrations were well above those necessary to inhibit cytomegalovirus. Pharmacokinetic parameters remained stable throughout the study. On day 14, the mean half-life was 3.4 h, total and renal clearances were 118 and 92 ml/min, respectively, and the volume of distribution was 0.6 liter/kg. These data and previous clinical trials demonstrate that this more convenient dosage regimen can be safely used for patients with cytomegalovirus disease. The side effects were comparable to those reported with other dosage regimens, although no renal impairment was seen in this study, probably because of the hydration.

Foscarnet, a PP_i analog (trisodium phosphonoformate hexahydrate), selectively inhibits the DNA polymerase of human herpesviruses, including cytomegalovirus and the reverse transcriptase of human immunodeficiency virus (HIV) (2). Clinical studies have demonstrated the role of foscarnet in the treatment of cytomegalovirus disease complicating immunodeficiency diseases, including HIV infection (8, 11, 18, 21). Because of poor oral absorption, foscarnet is administered intravenously (20). Pharmacokinetic parameters of this drug have been established after either continuous intravenous infusion (15, 19, 20) or intermittent administration at a dosage of 60 mg/kg of body weight every 8 h (1, 7). Clinical experience suggests that the twice-daily administration of 90 mg/kg was as effective as the three-times-daily administration of 60 mg/kg (5, 12).

The aim of this study was to evaluate the pharmacokinetic properties of foscarnet after single and repeated administrations of the twice-daily dosage regimen, which is more convenient than the currently used continuous intravenous infusion or the three-times-daily regimen.

MATERIALS AND METHODS

Patients. Eleven AIDS patients were included in the study: five patients with cytomegalovirus retinitis, five with cytomegalovirus gastrointestinal disease, and one with biopsy-proven cytomegalovirus pneumonitis. Nine were Caucasian males, one was a black male, and one was a Caucasian female. The median age was 34 years, (range, 22 to 44 years), the mean weight was 61 ± 9 kg, and the mean serum creatinine level was 86 ± 21 μM. Mean creatinine clearance calculated by the method of Cockcroft and Gault (3) was 94 ± 29 ml/min. Patients' weights and serum creatinine concentrations did not change significantly during the 2-week study period, as shown in Table 1.

Study design. Patients received an infusion of 90 mg of foscarnet per kg twice daily for 2 weeks. Foscarnet was provided by Astra as a solution for infusion (24 mg/ml) in 500-ml bottles. Each infusion lasted 2 h. All patients were hydrated during each foscarnet infusion with 750 to 1,000 ml of a 0.9% saline solution to prevent renal-function impairment (4).

During and after the first infusion on days 1, 7, and 14, venous blood samples were drawn through an indwelling cannula at 0 (before the start of infusion), 1, 2 (end of infusion), 2.5, 3, 6, 8, and 12 h. On the same days, urine was collected during the 12-h dosing interval. All blood samples (5 ml) were drawn in heparinized Venoject tubes, which were centrifuged immediately to separate plasma. Plasma and urine were heated at 56°C for 3 h in order to inactivate any HIV which may have been present in the samples; this process does not alter foscarnet (14). After decontamination, all biological samples were stored at −20°C until analyzed.

Assay method. Concentrations in plasma and urine were determined by a reversed-phase high-performance liquid chromatography assay with electrochemical detection according to a method described elsewhere (14). Plasma samples were injected directly onto the C18 column after dilution and ultrafiltration; prior to dilution, interfering compounds were removed from urine by treatment with activated charcoal.

The molecular weight of foscarnet is 300.1; therefore, the conversion factor from micromolarity to micrograms per milliliter is 0.3. The limit of sensitivity of the assay was 15 μM.

Interday coefficients of variation were 10 and 8% both for plasma samples spiked with 133 and 417 μM foscarnet,

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TABLE 1. Demographic and biological data of the 11 AIDS patients studied

Patient	Sex[a]	Age (yrs)	Weight (kg) on day:			S_{CR}[b] (μM) on day:			CL_{CR}[c] (ml/min) on day:		
			1	7	14	1	7	14	1	7	14
1	F	24	53	54	55	64	71	115	96	88	55
2	M	39	60	60	61	65	79	82	112	92	90
3	M	39	60	60	61	113	98	106	64	74	70
4	M	44	60	61	60	104	81	68	66	87	102
5	M	28	54	54	54	73	68	63	99	107	115
6	M	36	48	48	48	127	117		53	57	
7	M	30	70	72	72	84	75	95	116	134	105
8	M	38	79	77	76	66	68	107	145	137	86
9	M	44	53	57	55	100	81	82	64	85	81
10	M	43	68	70	68	81	81	107	97	100	73
11	M	35	69	64	68	74	99	95	125	87	96
Mean		36	61	62	62	86	83	92	94	95	87
SD		7	9	9	9	21	15	18	29	24	18

[a] F, female; M, male.
[b] S_{CR}, serum creatinine.
[c] CL_{CR}, creatinine clearance.

respectively, and for urine samples spiked with 40 and 125 μM foscarnet, respectively.

Pharmacokinetic analysis. Data were analyzed by noncompartmental methods (16).

The terminal-phase rate constant (λ_z) was determined by linear regression of the natural logarithms of the concentrations in plasma against time for the log-linear elimination phase typically from 3 through 12 h. Terminal half-life ($t_{1/2}$) was calculated by the following equation: $t_{1/2} = 0.693/\lambda_z$.

Area under the concentration-time curve from time 0 to the time (t) of the last sample (AUC_{0-t}) was calculated by the trapezoidal rule and extrapolated to infinity according to the following formula: $AUC_{t-\infty} = C_t/\lambda_z$, in which C_t is the concentration of the drug in plasma in the last sample, taken at time t.

The total clearance (CL) of the drug in plasma was calculated as follows: CL = dose/$AUC_{0-\infty}$ (for day 1) and CL = dose/AUC_{0-12} (for days 7 and 14), where AUC_{0-12} is the AUC from 0 to 12 h. The apparent volume of distribution (V_{area}) was calculated by the following formula: $V_{area} = CL/\lambda_z$.

Maximum concentration in plasma and time to maximum concentration of foscarnet were observed values.

The fraction (Fe) of the dose of foscarnet that was excreted unchanged in urine was calculated with the following equation: Fe = Ae/dose, in which Ae is the total amount of unchanged foscarnet excreted in 12 h. Renal clearance (CL_R) was calculated according to the following formula: $CL_R = Ae_{0-t}/AUC_{0-t}$, in which Ae_{0-t} is the amount of foscarnet excreted in t hours.

Average concentration at steady state (C_{av}) was assessed according to the following equation: $C_{av} = AUC_{0-12}/12$, with 12 h as the dosing interval.

The accumulation of foscarnet was evaluated by the following ratio: AUC_{0-12} (day 7 or 14)/AUC_{0-12} (day 1), where AUC_{0-12} values are those obtained following the first dose (day 1) and at steady state (days 7 and 14).

Statistical analysis. All results are expressed as means ± standard deviations. Correlation coefficients between pharmacokinetic parameters and creatinine clearance were determined by regression analysis.

RESULTS

Mean profiles of concentrations in plasma versus time for foscarnet after a single infusion and 1 or 2 weeks of treatment are compared in Fig. 1. No significant difference in concentrations in plasma after single-versus multiple-dose administration was observed. Wide ranges of peak and trough concentrations were observed with the 11 patients, as depicted in Fig. 2. Pharmacokinetic parameters are listed in Table 2. Mean peak concentrations were 581,577, and 605 μM on days 1, 7, and 14, respectively. Mean trough concentrations, 12 h after infusion, on days 7 and 14 were only slightly higher (38 and 52 μM, respectively) than after the first dose (33 μM), indicating that foscarnet did not accumulate in this 2-week period; accumulation ratios on days 7 and 14 were 0.87 ± 0.22 and 1.22 ± 0.41, respectively. All other pharmacokinetic parameters as well as the renal function remained unchanged throughout the study.

Because of the narrow interval of creatinine clearance, no

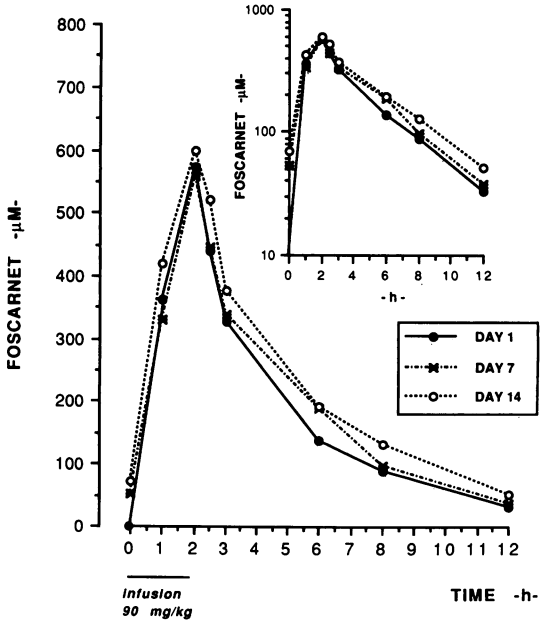

FIG. 1. Mean foscarnet concentrations in plasma versus time on days 1, 7, and 14 of therapy.

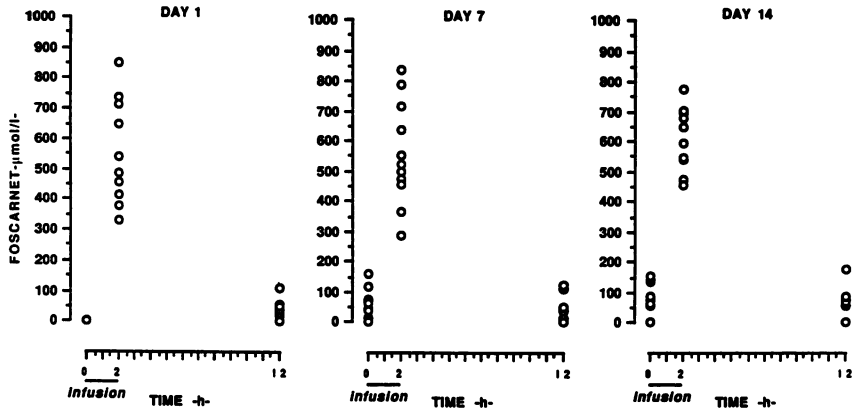

FIG. 2. Individual concentrations of foscarnet at the end of an infusion (2 h) and before the next infusion on days 1, 7, and 14 of therapy.

correlation could be established between renal clearance of foscarnet and the renal function quantitated with creatinine clearance or serum creatinine level.

DISCUSSION

The pharmacokinetic parameters of foscarnet (half-life, clearance, renal clearance, and volume of distribution) measured in this study are in agreement with those previously reported after either continuous (15, 19, 20) or intermittent (1, 7) infusion.

Figure 2 shows that interindividual variation of concentrations was high. Such variability has already been described: during continuous intravenous infusion of 230 mg/kg/day for 10 to 21 days, steady-state concentrations of foscarnet in plasma ranged from 75 to 458 μM in 19 HIV patients (19, 20) and from 164 to 529 μM in 13 AIDS patients with cytomegalovirus retinitis (6). According to Sjövall et al. (19, 20), the wide variation in foscarnet concentration in plasma within and between patients during continuous infusion may be, at least partly, the result of an interaction between foscarnet and phosphate with respect to their incorporation and sequestration into bone and of variations in renal elimination due to variations in polyuria.

The same variability exists after discontinuous administration: after 14 days of treatment with 60 mg/kg three times daily in eight AIDS patients with cytomegalovirus retinitis, maximal and minimal steady-state concentrations of foscarnet in plasma ranged from 272 to 699 (495 ± 149) μM and from 57 to 225 (126 ± 59) μM, respectively (means and standard deviations in parentheses) (1).

In our patients, there was little variation within each individual, which corroborates the results of other authors (1, 6).

As a consequence of the short plasma half-life, no accumulation occurs (accumulation ratio, 0.8 to 1.2), and maximal and minimal concentrations of foscarnet in plasma measured after the last administration are not significantly different from those measured after the first administration. The lack of accumulation demonstrates that the long half-life (36 to 196 h) estimated from the urinary excretion is not pharmacokinetically relevant (19).

As shown in Fig. 3, steady-state concentrations of foscarnet in plasma during continuous intravenous infusion of 230 mg/kg in 32 patients (6, 19, 20) and intermittent intravenous infusion of 60 mg/kg three times daily (1) or 90 mg/kg twice daily (this study) are in the same range. For these three dosage regimens, mean steady-state foscarnet concentrations in plasma are 228 ± 119 (19), 243 ± 129 (1), and 218 ± 86 μM, respectively. From a pharmacokinetic point of view, these three dosage regimens are comparable, but continuous infusion is not convenient for patients; furthermore, twice-daily administration could be more easily performed at home for outpatients (9).

The 50% effective concentration of foscarnet in vitro is approximately 130 μM against human cytomegalovirus and about 25 μM against HIV (2, 13, 17). In the treatment of cytomegalovirus retinitis, most investigators have aimed to maintain the foscarnet concentration in plasma within the range of 100 to 500 μM to ensure that effective antiviral levels are sustained (2). These concentrations are obtained with continuous infusion of 230 mg/kg/day. Intermittent infusion of foscarnet at dosages of 60 mg/kg every 8 h or 90 mg/kg every 12 h gave mean steady-state concentrations in plasma which were within the in vitro antiviral range. But in 3 of 8 patients treated with 60 mg/kg three times daily (1) and in 7 of 11 patients treated with 90 mg/kg twice daily (this study), individual trough levels were below 100 μM after 2

TABLE 2. Foscarnet pharmacokinetics in 11 AIDS patients[a]

Day	C_{max} (μM)[b]	C_{min} (μM)[c]	C_{av} (μM)	$t_{1/2}$ (h)	CL		CL_R (ml/min)	V_{area} (liter/kg)	Fe (% of dose)
					ml/min	ml/min/kg			
1	581 ± 161	33 ± 34		3.0 ± 1.2	121 ± 40	2.0 ± 0.6	86 ± 45	0.51 ± 0.21	69 ± 26
7	577 ± 182	38 ± 49	207 ± 107	3.0 ± 1.4	133 ± 63	2.3 ± 1.2	115 ± 43	0.57 ± 0.21	89 ± 17
14	605 ± 118	52 ± 59	218 ± 86	3.4 ± 1.4	118 ± 48	2.0 ± 0.6	92 ± 39	0.60 ± 0.22	84 ± 25

[a] Means ± standard deviations. C_{max}, C_{min}, and C_{av}, maximum, minimum, and average (steady-state) concentrations, respectively, of foscarnet in serum; $t_{1/2}$, half-life; CL, clearance; CL_R, renal clearance; V_{area}, volume of distribution; Fe, fraction of the dose of foscarnet that was excreted unchanged in urine in 12 h.
[b] Conversion factor for micrograms per milliliter, 0.30.
[c] Measured 12 h after infusion.

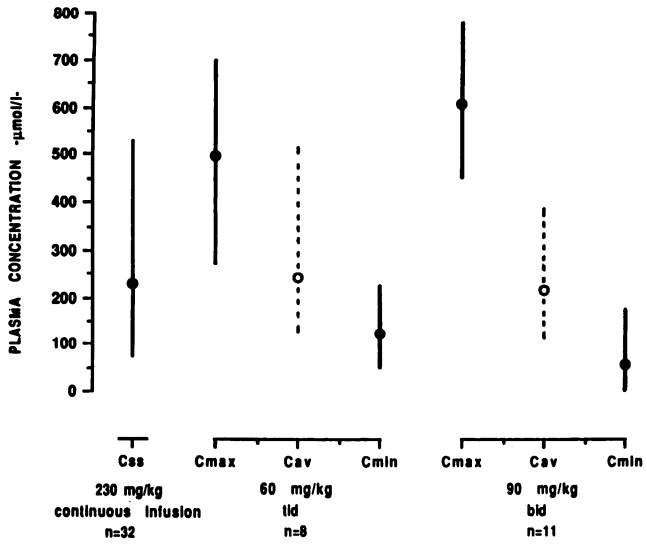

FIG. 3. Steady-state concentration (C_{ss}) of foscarnet in plasma during continuous infusion of 230 mg/kg in 32 patients (data from references 6, 19, and 20) and maximum (C_{max}), minimum (C_{min}), and average (C_{av}) concentrations of foscarnet during intermittent administration on day 14 of 60 mg/kg three times daily (tid) (1) or 90 mg/kg twice daily (bid) (this study). Circles, means; bars, range of data.

weeks of treatment. Nevertheless, clinical experience attests to the efficacy of these dosage regimens in the treatment of cytomegalovirus disease (5, 10, 12). It should be pointed out that with these intermittent dosages, mean minimal steady-state concentrations of foscarnet in plasma are above the in vitro 50% effective concentration for HIV.

One of the major drawbacks in the use of foscarnet is its nephrotoxicity (4). It is therefore of great interest that none of the patients in this study experienced any significant deterioration in their renal function. This lack of nephrotoxicity might be due to the saline loading during infusion. Alternatively, it might be due to the reduced dose fractionation. Renal dysfunction appears to be less severe and less prevalent during intermittent dosing than during continuous infusion (2, 10). However, in this study, hydration and reduced dose fractionation were performed simultaneously, so it is impossible to ascertain the exact cause of the lack of nephrotoxicity.

In conclusion, this investigation demonstrates that a 90-mg/kg twice-daily dosage regimen leads to mean concentrations of foscarnet in plasma which are above those necessary to inhibit cytomegalovirus. This dosage is more convenient for patients than continuous infusion or the commonly used 60-mg/kg three-times-daily regimen, especially for outpatients treated at home. Using this regimen with saline hyperhydration appears to allow the use of foscarnet without appreciable nephrotoxicity, and adverse effects are similar to those reported with other dosage regimens.

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