ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1989, p. 1023–1031
0066-4804/89/071023-09$02.00/0

Vol. 33, No. 7

Pharmacokinetics of Foscarnet and Distribution to Cerebrospinal Fluid after Intravenous Infusion in Patients with Human Immunodeficiency Virus Infection

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Received 13 December 1988/Accepted 5 April 1989

To investigate the pharmacokinetics and effects of intravenous foscarnet, 13 relatively healthy male patients with human immunodeficiency virus infection and a mean $CD4^+$ lymphocyte value of 0.45×10^{-9} cells per liter were given a continuous intravenous infusion of foscarnet (0.14 to 0.19 mg/kg per min) for 8 to 21 days. Blood and urine samples were taken during and after drug administration to monitor foscarnet concentrations. Lumbar puncture was performed during the infusion in five patients. The concentrations in plasma showed large variations both within and between patients. The disposition of foscarnet could be explained by a triexponential equation ($t_{1/2\lambda_1}$, 0.40 to 2.52 h; $t_{1/2\lambda_2}$, 3.20 to 16.7 h; $t_{1/2\lambda_3}$, 36 to 196 h). Renal clearance accounted for most of the plasma clearance, the difference probably reflecting the passage of foscarnet into bone. Up to 20% of the cumulative dose may have been deposited in bone 7 days postinfusion. Foscarnet was distributed to the cerebrospinal fluid in a concentration varying from 13 to 68% of the simultaneous concentration in plasma. Polyuria and polydipsia were recorded in all patients. There appears to be an association between the degree of malaise, including symptoms such as nausea, vomiting, fatigue, and headache, and concentrations in plasma above 350 μmol/liter.

Foscarnet (trisodium phosphonoformate hexahydrate) is an antiviral drug active in vitro against all human herpesviruses including cytomegalovirus (CMV) at concentrations of 100 to 300 μmol/liter (10) and against human immunodeficiency virus (HIV) (13, 14). Its mode of action is by selective inhibition of herpesvirus DNA polymerases as well as the HIV reverse transcriptase at concentrations not affecting normal cell growth (10).

Intravenous foscarnet may reduce the proportion of positive HIV cultures after treatment compared with that before treatment (4) and reduces the ability to detect HIV antigen in serum during treatment (1, 5, 8) in patients with the acquired immunodeficiency syndrome and the acquired immunodeficiency syndrome-related complex. Clinical experience in patients treated with intravenous foscarnet for opportunistic CMV infections suggests a beneficial effect (9, 12, 20).

Foscarnet is rapidly cleared from blood and other soft tissues in different animal species, but studies in mice show that about one-third of a parenteral dose is retained in bone and cartilage without any biotransformation (7).

Owing to poor oral absorption (17), the concentrations achieved in plasma after oral dosing have been considered too low for inhibition of HIV or CMV replication in vivo compared with the required in vitro inhibitory concentration of foscarnet (10, 13, 14). Thus, foscarnet must be administered intravenously.

This study was performed from March 1985 to May 1986 and was part of a project to evaluate intravenous foscarnet in the treatment of patients with culture-proven HIV infection to gather further pharmacokinetic knowledge of its disposition and effects in humans.

MATERIALS AND METHODS

Patients. Fourteen male patients entered the study. They were between 20 and 42 years old, with lymphadenopathy syndrome ($n = 11$) or acquired immunodeficiency syndrome-related complex ($n = 3$) with a positive blood culture of HIV and antibodies against HIV in serum confirmed by Western blotting (immunoblotting) (Table 1). The mean $CD4^+$ lymphocyte value was 0.45×10^{-9} cells per liter. Despite some symptoms such as fatigue, night sweats, and periods of loose stools, all patients with lymphadenopathy syndrome were working full time and had no history of weight loss before entering the study. All had normal creatinine levels in serum before treatment and had no evidence or history of renal, serious hepatic, or serious cardiovascular disease and were considered to be in satisfactory nutritional condition. Diuretics were not allowed during the study.

The creatinine levels in serum were used to estimate creatinine clearance (CL_{CR}) by the formula given by Cockcroft and Gault (2). The body surface area was calculated by the formula of Du Bois and Du Bois (3).

Concomitant drugs administered during foscarnet treatment were analgesics, benzodiazepins, and occasionally dimenhydrinate.

Experimental design. Each patient received a continuous intravenous infusion of foscarnet in a peripheral vein for up to 21 days, aiming at a steady-state concentration in plasma on the order of 450 μmol/liter. Plasma samples were collected during infusion as well as for 6 days postinfusion.

Drug and dosage. Foscarnet solution for intravenous infusion (2.4%, batch LF 1415) was provided in 500-ml bottles.

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TABLE 1. Patient characteristics

Patient no.	Age (yr)	Ht (cm)	Wt (kg)	Body surface area (m^2)	$CD4^+$ (cells, 10^{-9}/liter)	Creatinine level in serum (μmol/liter)	
						Initial	End of treatment
1	42	172	83	1.96	0.14	99	
2	31	164	60.5[a]	1.66	0.07	91	129
3	26	168	53.5	1.60	0.70	72	86
4	29	170	70	1.81	0.59	90	173
5	36	188	82	2.08	0.33	78	94
6	30	180	65	1.83	0.67	82	86
7	34	176	79	1.95	0.55	88	100
8	30	176	61	1.75	0.47	83	118
9	39	171	67	1.78	0.30	78	108
10	29	181	69	1.88	0.50	94	162
11	33	184	65	1.86	0.19	79	138
12	33	180	64	1.82	0.63	60	80
13	20	183	65	1.85	0.75	92	102
14	35	182	75	1.96	0.40	95	116
Mean	32	177	69	1.84	0.45	84	115
SD	6	7	9	0.13	0.22	11	29

[a] Body weight decreased to 56 kg during treatment.

The solution was diluted to 1.2 to 1.09% with 5% dextrose before administration to reduce the risk of thrombophlebitis.

Foscarnet was administered as a continuous intravenous infusion (0.14 to 0.19 mg/kg per min) with an infusion pump (Imed 960; Imed Scandinavia, Stockholm, Sweden) for 8 to 21 days.

Sampling. The start of infusion was time zero. Blood was collected from an arm vein by the heparin-lock technique with an indwelling catheter or by direct puncture with Venoject tubes (5 ml, containing heparin). The cannula and arm used for the most recent infusion were not used for sampling.

Samples of 4 ml each were drawn just prior to dosing and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h and thereafter every 24 h during the whole infusion period. On day 10 or 14, additional samples were taken every 4 h between 8 a.m. and 8 p.m.

Samples of 4 to 5 ml were taken at the time infusion was stopped and 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 60, and 72 h after the end of infusion and thereafter every 24 h for 6 days postinfusion.

Urine was collected at 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after the start of infusion. Thereafter, every 12 h during infusion, the times were selected so that the plasma sample was taken at the end of the collection interval.

In the postinfusion period, urine samples were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 18, 18 to 24, 24 to 36, 36 to 48, and 48 to 72 h after the end of infusion. Thereafter, the total urinary output was collected every 24 h for 3 additional days.

In five patients, cerebrospinal fluid (CSF) was collected for determination of spinal fluid characteristics, HIV culture, and HIV antibodies. These samples were also used to assay for foscarnet.

Assay procedure. Before the plasma and urine samples were delivered to Astra Alab AB, they were subjected to three independent steps, each of which eliminates any infectious virus. These steps consisted of ultrafiltration (Centricon 30; Amicon Corp., Lexington, Mass.), addition of anhydrous ethanol (1/9, vol/vol), and heating to 56°C for 30 min. The main reason for ultrafiltration is to remove the proteins from plasma and is, for noninfectious plasma samples, the only pretreatment that is necessary. Before the ultrafiltration, urine was treated with activated charcoal to eliminate interfering endogenous compounds.

Phosphonoformic acid was determined in the ultrafiltrate by reversed-phase liquid chromatography with electrochemical detection at Astra Alab AB, Södertälje, Sweden, by the method of Pettersson et al. (11). The limit of determination was 33 μmol/liter, and the precision calculated as the coefficient of variation was 5% at 300 μmol/liter.

Pharmacokinetic calculations. The pharmacokinetic parameters of foscarnet were estimated by a nonlinear least-squares regression analysis (15) on the concentrations in plasma during and after cessation of infusion by means of a two- and three-compartment model (6). In a linear multicompartment model, the concentration in plasma (C_p') during (0, T) and after (T, ∞) intravenous infusion can be described by the following function of time (t):

$$C_p^{\,t} = \begin{cases} \sum_{i=1}^{j} C_i'(1 - e^{-\lambda_i t}), \text{ if } 0 \le t \le T \\ \qquad\qquad \text{(during infusion); } j = 2, 3 \\ \sum_{i=1}^{j} C_i'(e^{-\lambda_i (t-T)} - e^{-\lambda_i t}), \text{ if } t > T \\ \qquad\qquad \text{(after infusion); } j = 2, 3 \end{cases}$$

where T is time for end of infusion and λ_i is the first-order disposition rate constant of the exponential phase of the curve. Initial parameter values for the regression analysis were estimated postinfusion by nonlinear regression on the concentrations in plasma and linear regression on the terminal urinary excretion rates. The estimated disposition rates were held constant in the subsequent nonlinear regression analysis. The zero-time intercept, C_i, was related to C_i' according to $C_i = C_i' T\lambda_i$.

Total area under the plasma concentration-time curve (AUC) after intravenous infusion was estimated from the parameters obtained by nonlinear regression (6). Plasma half-life ($t_{1/2\lambda_i}$) and total plasma clearance (CL_T) were estimated as $\ln 2/\lambda_i$ and (infusion rate × T)/AUC, respectively. The fraction of foscarnet excreted unchanged in urine at apparent steady state (f_e) was calculated as the amount of foscarnet excreted in the urine during the interval (t, $t + dt$) divided by the infusion rate. Renal clearance (CL_R), nonrenal clearance (CL_{NR}), the renal filtration clearance (CL_{RF}), and the net renal secretion clearance (CL_{RS}) were estimated from $CL_R = f_e \times CL_T$; $CL_{NR} = CL_T - CL_R$; $CL_{RF} = CL_{CR} \times f_u$; $CL_{RS} = CL_R - CL_{RF}$, where f_u is the free fraction of foscarnet in plasma (83% according to J. Lundström, personal communication). The apparent volume of distribution at steady state (V_{ss}) and of the central compartment were calculated from the parameters obtained by nonlinear regression (6). When possible, three components (C_i, λ_i) were used when estimating the parameters; otherwise, two components were used.

Statistical methods. Changes in creatinine with time and changes in CL_R with urine flow within each patient are dependent but were assumed to be independent between patients. In the current model, these variables were modeled as a linear function of time. Classical least-squares regression was used with the data from each patient to estimate the slope. Thus, independent slopes were obtained which constituted our random variables. A one-sample sign rank test

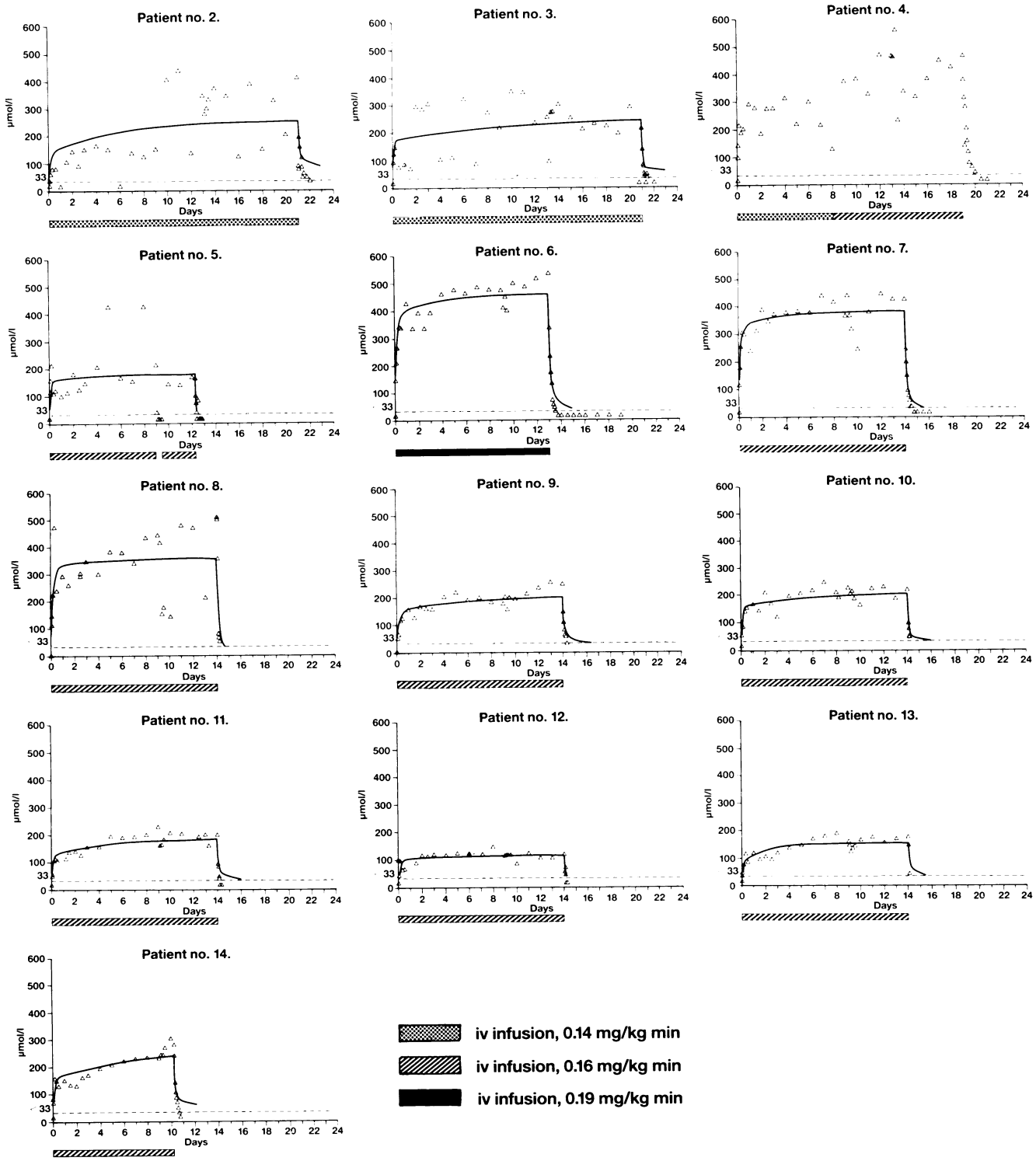

FIG. 1. Concentrations of foscarnet in plasma of 13 HIV-infected patients given continuous intravenous infusion of foscarnet. —, Estimates from nonlinear regression analysis.

was employed. When testing creatinine levels in serum, the hypothesis was that the median slope of the distribution underlying the sample was less than or equal to zero, against the alternative that the median slope was positive. As regards estimated CL_{CR} and CL_R, the hypothesis was that the median slope was greater than or equal to zero, against the alternative that the median slope was negative.

RESULTS

Treatment was interrupted in patient 1 after 1 week on foscarnet owing to psychiatric and physical problems not considered to be drug related. The patient was therefore excluded from the pharmacokinetic evaluation. This report is thus based on the results from 13 patients. Patient 4

TABLE 2. Pharmacokinetic parameters during and after continuous intravenous infusion of foscarnet in 13 patients with HIV infection

Patient no.	Infusion rate (k_0)		Infusion time (h)	$t_{1/2\lambda_1}$ (h)	$t_{1/2\lambda_2}$ (h)	$t_{1/2\lambda_3}$ (h)	Estimated C_p^{ss} (μmol/liter)
	mg/kg per min	μmol/kg per min					
2	0.14	0.47	503.6	2.0	16.7	98	255
3	0.14	0.47	503.9	1.1		196	243
4	0.14	0.47	191.8				
	0.16	0.53	263.4	0.4	6.2	64	
5	0.16	0.53	294.3	1.4		86	180
6	0.19	0.63	311.8	1.1	4.5	60	458
7	0.16	0.53	335.8	0.8	4.8	55	381
8	0.16	0.53	335.7	1.3	3.2	53	356
9	0.16	0.53	335.9	0.8	5.5	131	201
10	0.16	0.53	335.8	1.5		95	205
11	0.16	0.53	335.8	1.4		69	184
12	0.16	0.53	336.1	2.5	4.6	82	115
13	0.16	0.53	336.2	1.7		36	155
14	0.16	0.53	245.8	1.9		112	238
Mean	0.16	0.53		1.4	6.8	88	228
SD	0.01	0.04		0.6	5.0	42	119

received foscarnet at two different infusion rates; therefore, the nonlinear regression analysis was not applied to the results from this patient.

The concentrations in plasma rose rapidly during the first 24 h of intravenous infusion. After that, there was a slower increase in concentrations in plasma, with a large variation in concentrations both within and between patients, with concentrations in plasma on the order of 100 to 500 μmol/liter (Fig. 1). The largest variation was seen in patients 2 and 3. The highest concentrations in plasma were seen in patient 6, who received the highest dose, 0.19 mg/kg per min.

The $t_{1/2}$s, calculated from the disposition rate constants based on the concentrations in plasma postinfusion, varied for 0.4 to 2.5 h (λ_1 phase) and 3.2 to 16.7 h (λ_2 phase) (Table 2). A slower terminal disposition rate (λ_3 phase) was estimated from the urinary excretion rate versus time at late sampling times (Fig. 2). The terminal $t_{1/2}$ calculated from the postinfusion urinary excretion rate varied from 36 to 196 h (Table 2).

The concentrations in plasma during and after intravenous infusion were described by the three-compartment model in patients 6, 7, 8, 9, 10, and 12 and in the others by the two-compartment model. The mean value of the λ_2 disposition rate (Table 2) was successfully used in the regression analysis of the results from patients 10 and 12, in whom a λ_2 phase could not be estimated from concentrations in plasma postinfusion. In the other patients, patients 2, 3, 5, 11, 13, and 14, the two-compartment model was based on the initial phase (λ_1) and the terminal disposition rate was estimated from urinary excretion (λ_3). The estimated steady-state concentrations in plasma calculated from the model equations varied from 115 to 458 μmol/liter (Table 2).

The fraction of foscarnet dose excreted unchanged in the urine at apparent steady state, during the last 1 or 2 days of infusion, varied from 0.79 to 0.92 (Table 3). CL_R therefore accounted for most of the plasma clearance. Thus, foscarnet is mainly eliminated by the kidneys. The total CL_R exceeded the CL_{RF} in all patients but one. The mean (± standard deviation) glomerular filtration and net tubular secretion of foscarnet were, respectively, 58 ± 22% and 42 ± 22% of CL_R. The CL_R increased with an increase in urine flow with a median slope of 0.38 ($P < 0.01$).

The V_{ss} was large (Table 3). V_{ss} increased markedly with a decrease in the disposition rates (λ_i) and an increase in the number of exponents used in the calculations. As expected, no such effect was seen in the estimates of the volume of the central compartment.

The CSF was examined in five patients (Table 4). It had a normal appearance as regards cells and glucose in all patients. The protein concentration was slightly increased in three patients and markedly increased to 1.4 g/liter in one patient, suggesting a meningeal barrier defect. Tests for HIV antibodies and HIV culture were consistently negative. The mean (± standard deviation) distribution ratio of foscarnet in CSF versus plasma in samples taken within 15 min of CSF

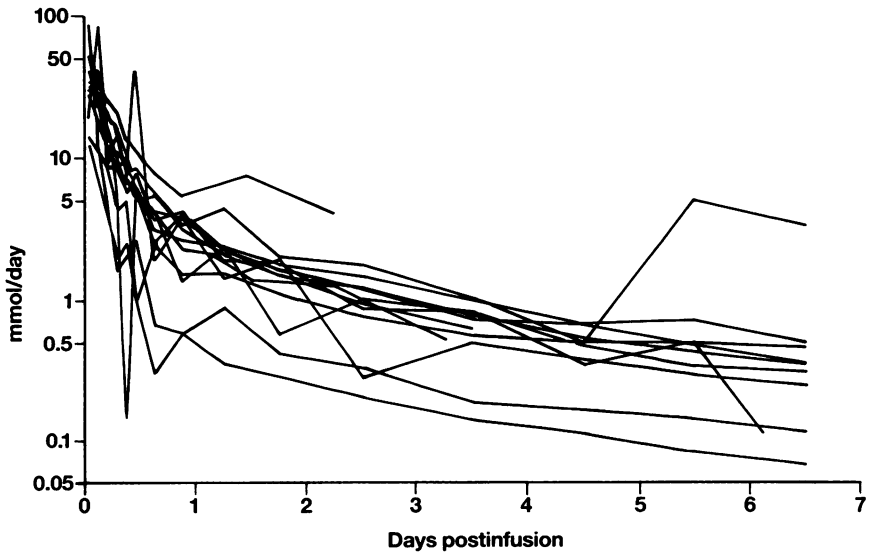

FIG. 2. Urinary excretion rate versus time postinfusion after continuous intravenous infusion of foscarnet in 13 patients with HIV infection.

TABLE 3. Pharmacokinetic parameters after continuous intravenous infusion of foscarnet in 13 patients with HIV infection

Patient no.	CL_T (ml/min per 1.73 m^2)	CL_{NR} (ml/min per 1.73 m^2)	CL_R (ml/min per 1.73 m^2)[a]	f_e[a,b]	CL_{RF} (ml/min per 1.73 m^2)	CL_{RS}[c] (ml/min per 1.73 m^2)	V_1 (liter/kg)	V_{ss} (two-compartment model) (liters/kg)	V_{ss} (three-compartment model) (liters/kg)
2	114	12	102 (2)	0.90 (0.02)	55	47	0.58[d]		7.4[d]
3	105	14	91 (30)	0.87 (0.29)	76	15	0.25[d]		10.2[d]
4				0.87 (0.07)	64				
5	199	41	158 (16)	0.79 (0.08)	77	81	0.42[d]		3.2[d]
6	85	12	73 (5)	0.86 (0.06)	78	−5	0.21	0.33	1.3
7	98	10	88 (8)	0.90 (0.08)	70	18	0.16	0.31	1.2
8	90	11	79 (10)	0.88 (0.10)	55	24	0.45	0.45	0.9
9	165	21	144 (18)	0.87 (0.11)	60	84	0.45	1.00	7.9
10	162	27	135 (36)	0.83 (0.22)	73	61	0.46	0.48	5.5
11	173	19	154 (32)	0.89 (0.18)	58	96	0.53[d]		6.0[d]
12	282	22	260 (26)	0.92 (0.09)	81	179	1.15	1.16	4.8
13	210	30	180 (22)	0.86 (0.11)	71	109	0.87		5.1[d]
14	136	26	110 (35)	0.81 (0.26)	59	51	0.56		8.1[d]
Mean	152	20	131	0.87	67	63	0.51	0.62	5.1
SD	59	9	53	0.04	9	51	0.28	0.36	3.0

[a] Parentheses represent standard deviation within patients.
[b] f_e, Fraction excreted unchanged in urine at apparent steady state.
[c] CL_{RS}, Net renal secretion clearance.
[d] Based on C_1, λ_1, C_3, and λ_3.

sampling was 43 ± 19%. The distribution seems rather rapid since a CSF concentration of 77 μmol/liter (68% of that in plasma) was already achieved on day 2 of treatment in patient 11.

The net amount of foscarnet not excreted in the urine was calculated as the difference between cumulative dose and cumulative amount excreted in the urine during and after infusion. Assuming that foscarnet is eliminated from the body solely by the kidneys, Fig. 3 shows the amount of drug retained in each patient up to 2 to 8 days postinfusion. A slow terminal elimination of foscarnet is indicated by the flat curve after the end of infusion. The fraction of the intravenous dose not excreted in the urine 7 days after end of infusion varied from 3 to 20% (mean, 12%; standard deviation, 5.6).

Creatinine levels in serum were usually within normal limits but increased slightly during treatment (Table 1) with a median slope of 0.73, which was significantly different from zero ($P < 0.01$). Similarly, the estimated CL_{CR} decreased with a median slope of −0.44 ($P < 0.01$) (Fig. 4). An effect was also seen on levels of phosphate in serum, which decreased during the first days of infusion, thereafter increased, and then decreased after the end of the intravenous infusion (Fig. 5).

Headache was reported in 12 patients and nausea in 10 of the 13 patients (Table 5). Three patients experienced pain from the kidney region. Mild to moderate thrombophlebitis was seen in six patients.

Toward the end of treatment, symptoms such as nausea, fatigue, and headache and a very clear deterioration of general condition such as paleness, malaise, and a reluctance to rise from bed were especially pronounced in patients 2, 4, 6, 8, 10, and 14. Of these, the first four patients had high concentrations in plasma (>350 μmol/liter) for at least 4 days.

Patient 10 was bedridden after lumbar puncture with severe headache and nausea. He was depressed and consumed large quantities of benzodiazepins. His concentrations in plasma were <350 μmol/liter, and the headache may be explained by the lumbar puncture. Patient 14 discontinued treatment on day 11, after 2 days of severe malaise with vomiting accompanied by rapidly rising concentrations in plasma and creatinine levels in serum, although his maximum concentrations in plasma only reached 300 μmol/liter. Patient 5 temporarily discontinued treatment on day 10 because of abdominal pain, diarrhea and nausea. His concentrations in plasma had two single values of >400 μmol/liter, but otherwise the concentrations in plasma were con-

TABLE 4. CSF characteristics and foscarnet concentration and concentration in plasma during continuous intravenous infusion of foscarnet in five patients with HIV infection

Patient no.	Treatment day no.	CSF					Plasma concn (μmol/liter)	Ratio CSF/plasma concn
		Cells and glucose	Protein (g/liter)	HIV		Foscarnet concn (μmol/liter)		
				Culture	Intrathecal antibody production			
6	8	Normal	0.55	Not done	Not done	63	477	0.13
10	8	Normal	Normal	Negative	Negative	67	193	0.34
11	2	Normal	Normal	Negative	Negative	77	113	0.68
	13	Normal	0.53	Not done	Not done	80	160	0.50
12	7	Normal	0.40	Negative	Negative	47	120	0.39
13	9	Normal	1.40	Not done	Negative	77	147	0.52

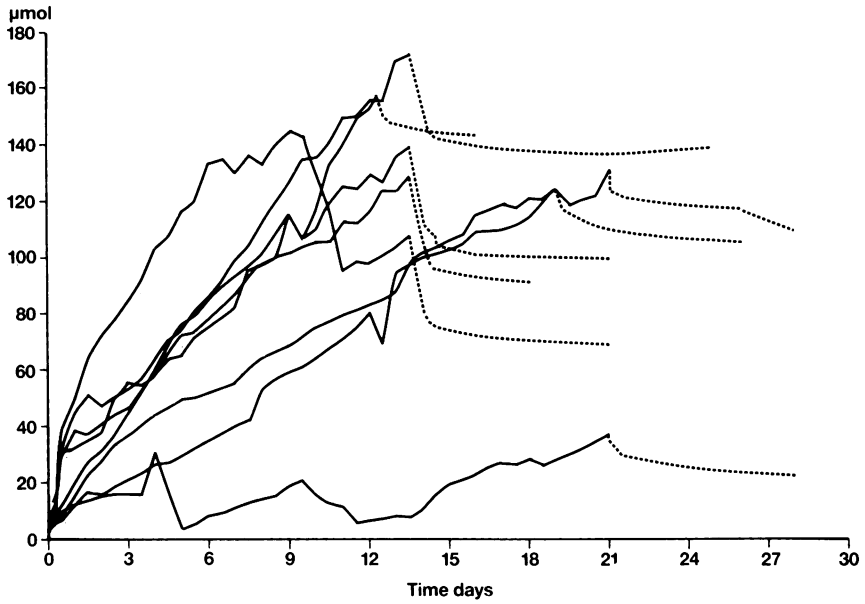

FIG. 3. Cumulative amount of foscarnet not recovered in urine during and after continuous intravenous infusion of foscarnet in eight HIV-infected patients. ----, After end of infusion.

sistently below 220 μmol/liter. Treatment was finally discontinued on day 13 because of the same reaction. Patient 7 had high concentrations in plasma, >350 μmol/liter, during most of the treatment. He complained about headache and fatigue but did not appear as sick as the others with high concentrations in plasma.

Thus, there appears to be an association between the degree of malaise, including symptoms such as nausea, vomiting, fatigue, and headache, and concentrations in plasma above 350 μmol/liter.

Most adverse events were tolerable, intermittent, and varying in severity during treatment. In six patients, symptoms got constantly worse over time from week two of treatment.

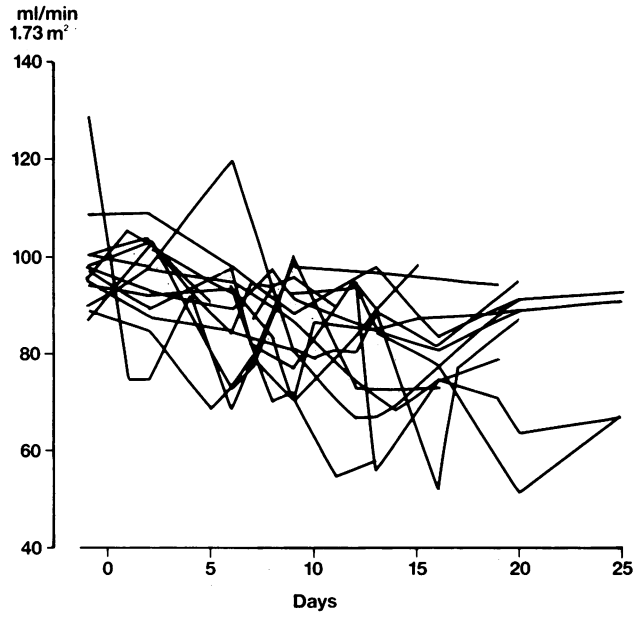

FIG. 4. Estimated CL_{CR} during and after continuous intravenous infusion of foscarnet in 13 HIV-infected patients.

Large urinary volumes were recorded in all patients (Table 6) and, as expected, were often combined with a high fluid intake and complaints of thirst (Table 5). In patients 7, 11, and 13, 24-h urinary volumes of 7 to 8 liters were recorded. There were no marked changes in body weight during treatment.

DISCUSSION

A high correlation has been found between plasma clearance of foscarnet and renal function (1/serum creatinine) with a zero intercept, indicating that foscarnet is mainly eliminated by the kidneys (J. Sjövall, unpublished data). These results as well as studies in animals (J. Lundström, personal communication) suggest that there is no quantitatively important metabolic conversion of foscarnet. Still, the CL_{NR} of foscarnet in this study varied between 10 and 58 ml/min per 1.73 m^2. A probable explanation for this is that the extrarenal clearance reflects an uptake of foscarnet into bone tissue.

Up to 20% of the cumulative intravenous dose had not been excreted in the urine 7 days after the end of infusion and can be assumed to have been deposited in bone (Fig. 3). These results are in accordance with the amount of foscarnet shown to be retained in the skeleton of animals (10).

The V_{ss} was on the order of 1.0 to 10 liters/kg, which represents 2 to 20 times that of the total body water. When only the two first disposition rates (λ_1, λ_2) were used in the calculations, V_{ss} was markedly underestimated compared with estimates based on the three-compartment model.

The apparent volume of the central compartment, 0.51 liters/kg, was, as expected, not influenced by the number of exponents used in the calculations.

Four of five patients had slightly elevated protein levels in the CSF, in accordance with previous observations in this patient category. Foscarnet was efficiently distributed to the CSF. A barrier defect in these HIV-infected patients, as

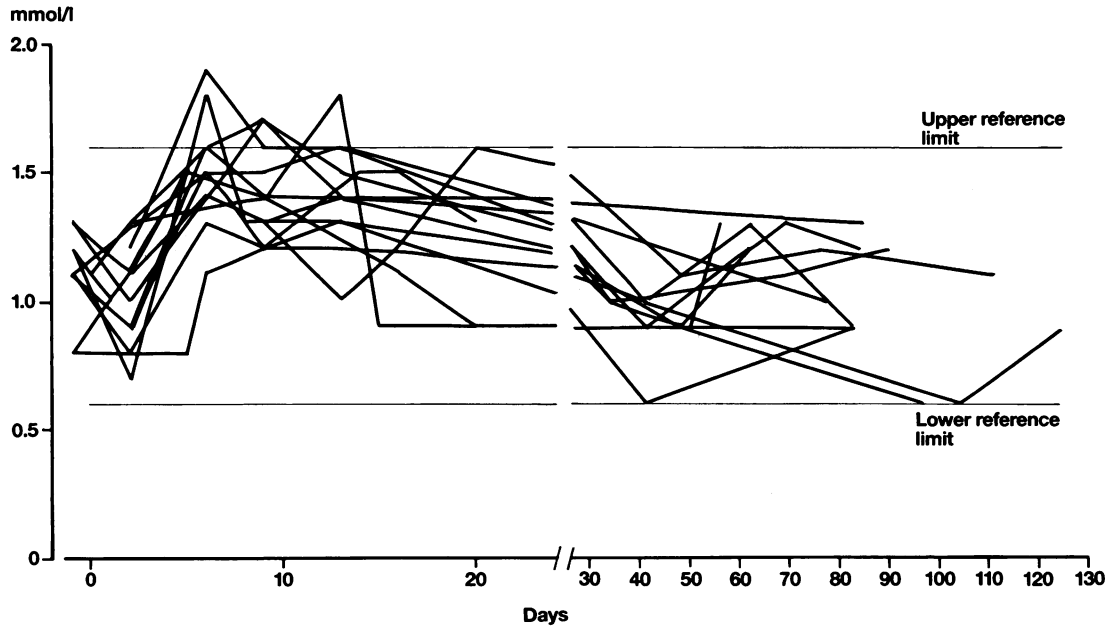

FIG. 5. Changes in phosphate levels in serum in 13 HIV-infected patients given a continuous intravenous infusion of foscarnet.

reflected by the increased protein, may have contributed to an increased passage of foscarnet.

Large urinary volumes were reported in all patients. The large variation in renal secretion clearance of foscarnet (Table 3) may be a consequence of polyuria leading to changes in CL_{CR}.

There is a substantial tubular secretion and reabsorption of creatinine. A large increase in the excreted fraction of creatinine has been reported following hydration, probably owing to an increased secretion and decreased reabsorption of creatinine (16). Another consequence of the large urinary volumes is probably a more variable CL_{CR} (Fig. 4).

In contrast to a previous report (17), the association between urine flow and CL_R in our study suggests that foscarnet is reabsorbed in the renal tubuli. The CL_R of drugs that are reabsorbed should be sensitive to changes in the urine flow (19).

The slight but significant increase in creatinine levels in serum during the study may have contributed to the increase in the concentration of foscarnet in plasma during infusion, as there is a high correlation between renal function and foscarnet clearance (J. Sjövall, unpublished data). The increase in creatinine levels in serum from 89 to 151 μmol/liter on day 7 to 12 in patient 14 probably explains the peak concentration of foscarnet in plasma seen just before the end of the infusion (Fig. 1).

Foscarnet has been shown to be a specific competitive inhibitor of the Na^+-phosphate cotransport in renal cortical brush border membrane vesicles of rats (18) and humans (21). The inhibition was dose dependent and specific for phosphate. The administration of foscarnet may therefore decrease the tubular reabsorption and thus increase the renal excretion of phosphate. Thus, the changes in phosphate levels in serum may be a reflection of the incorporation of foscarnet in bone and the interaction between foscarnet and renal elimination of phosphate.

Although foscarnet was given as a continuous intravenous infusion at a constant rate with an infusion pump, there was a large variation in concentrations in plasma of patients

TABLE 5. Adverse experiences in 13 patients with HIV infection given a continuous intravenous infusion of foscarnet

Adverse symptom	No. of patients
Nausea	11
Anorexia	9
Thirst	6
Vomiting	5
Malaise	3
Diarrhea	2
Colonic spasm	1
Headache	13
Fatigue	13
Fever	3
Loin pain	3
Thrombophlebitis	7

TABLE 6. Urinary volumes during continuous intravenous infusion of foscarnet in 13 patients with HIV infection

Patient no.	Mean vol (ml/12 h)	Minimum and maximum vol (ml/12 h)
2	1,626	462 and 2,798
3	1,507	823 and 2,282
4	1,881	932 and 2,902
5	1,755	801 and 3,044
6	2,152	1,377 and 3,068
7	3,511	1,761 and 4,870
8	2,013	1,224 and 2,439
9	1,954	1,096 and 2,655
10	2,120	1,130 and 3,513
11	2,542	1,044 and 4,940
12	2,257	1,430 and 3,279
13	2,516	1,040 and 4,146
14	1,577	950 and 2,722
Mean	2,109	
SD	353	

during the infusion. The method used for bioassay of foscarnet in plasma and urine has a high accuracy and precision, and foscarnet has been shown to be stable during pretreatment and storage (11). During the study, control samples containing known concentrations of foscarnet were regularly prepared and treated like the other samples to check the performance of the analytical system. The assay method is specific for foscarnet, and it is highly unlikely that the results of the assay were influenced by concomitant medication. Furthermore, there was little variation in the ascending and descending parts of the plasma concentration-time curves (Fig. 1). This indicates that the wide variation in concentrations in plasma during infusion cannot be ascribed to the assay method per se. The variation may be at least partly the result of a dynamic interaction between foscarnet and phosphate regarding their sequestration into bone and renal elimination. Patients with a lower apparent CL_{NR} (Table 3), probably reflecting less efficient uptake in bone, tended to have higher and more variable concentrations in plasma (Fig. 1) than patients with a higher CL_{NR}. Variations in polyuria (Table 6) may also have contributed to variations in the CL_R of foscarnet and consequently in concentrations in plasma.

The estimated two- or three-compartment model functions tended to overestimate the $t_{1/2}$ postinfusion in some patients (Fig. 1). This is probably due to poor estimates of the λ_2 phase, which could not be incorporated at all in some of the regression analysis. As a consequence of this, the effect of the longer terminal $t_{1/2}$ is overestimated at early time points postinfusion.

The apparent terminal $t_{1/2}$ in this study was longer than that reported in a pharmacokinetic study with a shorter follow-up period (17). A more extended sampling period and an assay method able to detect lower concentrations of foscarnet may show a still longer terminal $t_{1/2}$, approaching the release rate from bone. In patient 6, three samples of urine were collected at 12-h intervals 2.3 years posttreatment. By using a more sensitive high-pressure liquid chromatography assay, foscarnet was still detected in the urine at a concentration of >0.64 and <4.3 μmol/liter (A. Persson, personal communication). This supports the slow release of foscarnet from bone reported in animals. Therefore, AUC was probably underestimated in this study. Thus, the true values of the parameters dependent on AUC (plasma clearance, V_{ss}) are expected to be smaller and larger, respectively, than reported in this study if an extended sampling period is used.

A tendency of positive HIV blood cultures to decrease was seen in this study. Several patients reported a temporary relief of symptoms such as night sweats, general fatigue, and bowel disturbances. After these promising results, a controlled study in which foscarnet was given by intermittent intravenous infusions was initiated, showing an in vivo antiviral effect of foscarnet against HIV (S. Bergdahl, A. Sönnerborg, J. Albert, J. Sjövall, A. Larsson, M. Halvarsson, A. Aust-Kettis, B. Jakobsson, and Ö. Strannegård, Program Abstr. IVth Int. Conf. AIDS, Stockholm, abstr. no 3588, 1988).

The concentrations in plasma achieved with continuous intravenous infusion of foscarnet appear to be adequate for inhibiting CMV and HIV replication in vivo compared with the foscarnet concentration required for in vitro inhibition (10, 13, 14). Foscarnet was also shown to pass the blood-brain barrier, which is important because HIV affects the central nervous system. If given by intermittent infusion, the short $t_{1/2}$ of foscarnet ($\lambda_1 - \lambda_2$ phase) is probably relevant for prediction of the duration of antiviral effect, while the terminal $t_{1/2}$ reflects its accumulation and retention in bone tissue. The fact that foscarnet inhibits the replication of both CMV and HIV may give the drug a therapeutic advantage, as CMV infections with focal complications are common in AIDS patients.

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