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Pharmacokinetics of Intermittently Administered Intravenous Foscarnet in the Treatment of Acquired Immunodeficiency Syndrome Patients with Serious Cytomegalovirus Retinitis

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Foscarnet has been shown to be active in vitro against the human immunodeficiency virus and all human herpesviruses including cytomegalovirus (CMV). A pharmacokinetic study was carried out as part of a clinical trial designed to evaluate the safety and efficacy of intermittently administered intravenous foscarnet for the treatment of CMV retinitis. Eight patients with acquired immunodeficiency syndrome and serious CMV retinitis received 2-h intravenous infusions of foscarnet at a dosage of 60 mg/kg of body weight every 8 h for 14 days. Serial plasma samples were collected on days 3 and 14 of therapy, and foscarnet concentrations were determined by high-pressure liquid chromatography. On day 3 of therapy, the mean (± standard deviation) peak and trough levels in plasma were 509 (200) and 98 (29) μM, respectively, while on day 14 levels were 495 (149) and 126 (59) μM. The mean clearance in plasma on days 3 and 14 were 1.9 (0.6) and 1.7 (0.9) ml/min per kg, respectively. On day 14, the mean half-life was 4.5 (1.2) h and the volume of distribution was 0.74 (0.60) liter/kg. As the half-life and the clearance of foscarnet in plasma correlated with changes in renal function, dosage adjustments must be made for patients with decreased renal function.

Trisodium phosphonoformate (foscarnet) is an antiviral agent active in vitro against a variety of RNA and DNA viruses, including human herpesviruses and human immunodeficiency virus (9, 11, 12). Its antiviral effect is believed to be due primarily to selective inhibition of viral DNA polymerases or reverse transcriptase. Clinical experience with this agent has shown it to provide some benefit for the treatment of cytomegalovirus infections in immunocompromised patients such as bone marrow and renal transplant recipients (8) and patients with the acquired immunodeficiency syndrome (AIDS) (3, 7, 14). In addition, research under way to evaluate its effectiveness in treating underlying human immunodeficiency viral infection shows promising results (4, 6).

The pharmacokinetic disposition of foscarnet has previously been studied after continuous intravenous infusion (10, 13); however, this agent is currently being administered intermittently every 8 h as a 1- or 2-h infusion at a number of treatment sites (A. Larsson, Astra Lakemedal, unpublished data). It is believed that this mode of administration may help prevent the adverse effects reported in initial studies, such as infusion site thrombophlebitis and nephrotoxicity. The purpose of this investigation was to determine the pharmacokinetics of intermittently administered foscarnet in patients with AIDS during a 14-day course of therapy for cytomegalovirus retinitis.

MATERIALS AND METHODS

Foscarnet therapy. Enrollment in the study required a diagnosis of AIDS, as defined by the Centers for Disease Control, Atlanta, Ga., and symptomatic cytomegalovirus retinitis. Each subject was informed of the nature and risks of the investigation, and consent was obtained prior to participation. The study was approved by the University of California San Francisco Human Subjects Committee, an Investigational Research Bureau constituted according to U.S. Food and Drug Administration guidelines. Patients receiving ganciclovir or foscarnet were excluded from the study. Concomitant therapy with acyclovir or zidovudine was also restricted. A complete medical history, a physical examination, and a panel of laboratory tests consisting of a chemistry screen and a complete blood cell count with differential and platelet count were carried out before and after completion of the study. In addition, a 24-h creatinine clearance was obtained on days 3 and 14 of the study, when possible. For the majority of the patients, however, an approximation of creatinine clearance was made by using the equation of Cockcroft and Gault (2), due to difficulties in obtaining a complete urine collection. Patients with normal renal function were given foscarnet at a dose of 60 mg/kg of body weight every 8 h as a 2-h intravenous infusion for 14 days. Dosage adjustments were made for patients with decreased creatinine clearance according to guidelines based on preliminary pharmacokinetic data from Astra Alab AB, Södertälje, Sweden. Astra Alab provided foscarnet solution for infusion (24 mg/ml) in bottles of 500 ml. In the case of peripheral intravenous infusion, the solution was diluted in 5% glucose to a concentration of 12 mg/ml.

To study the pharmacokinetic disposition of foscarnet at steady state, serial blood and urine sampling was carried out on study days 3 and 14. Blood samples (4 ml each) were collected prior to the ninth dose (day 3) and at 0.25, 0.5, 1, 2, 3, 4, and 6 h after the end of the 2-h infusion. Blood samples were also collected prior to the last dose (day 14) and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 23 h after completion of the infusion. Each sample was collected in heparinized Sarstedt-monovette tubes, was placed immediately on ice, and was centrifuged. Plasma was harvested, stored in glass dram vials, and frozen at −20°C to await further processing. Urine was collected, and 10-ml samples were saved prior to drug administration and during the intervals 0 to 2, 2 to 4, and 4 to 8 h for most patients. An additional sample was collected

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from 8 to 12 h on day 14 of the study. Samples were stored in glass scintillation vials and were kept at −20°C.

Analytical methods. All plasma and urine samples were analyzed by Astra Alab, using reversed-phase liquid chromatography. Prior to shipment, all samples were processed and heat inactivated to assure inactivation of all human immunodeficiency virus. For processing, 1 ml of each sample was transferred to a micropartition tube (Centricon-30) and was centrifuged for at least 15 min to remove all plasma proteins and collect 200 μl of ultrafiltrate. The ultrafiltrate was placed in 2-ml plastic Sarstedt tubes which were subsequently placed in a boiling water bath for 20 to 30 min. Studies have shown that foscarnet is stable during the heat deactivation process (A. Larsson, unpublished data). All materials used for sample processing and storage were selected to assure that foscarnet would not adhere to the material surface. Foscarnet has been shown to be stable at −20°C for at least 3 years and for more than 4 days at room temperature (K. J. Pettersson and T. Nordgren, J. Chromatogr., in press).

Foscarnet levels were determined from the ultrafiltrate by Astra Alab, using reversed-phase liquid chromatography with electrochemical detection (13). The lowest concentration detectable was 33 μM (10 mg/liter), and the precision coefficients of variation ranged from 3 to 16% for plasma and 2 to 5% for urine throughout the concentration range.

Pharmacokinetic analysis. Noncompartmental pharmacokinetic analysis was used to determine the pharmacokinetic parameters of foscarnet (5). The half-life was calculated by dividing 0.693 by the terminal elimination rate constant (lambda z) obtained from the terminal phase of the plasma concentration-time curve. The area under the plasma concentration-time curve at steady state (AUC_{ss}) was calculated by using the log-trapezoidal rule over the dosing interval (time zero to 8 h) on days 3 and 14.

Estimates of the plasma clearance (CL) and the volume of distribution (V) were calculated by using the equations $CL = dose/AUC_{ss}$ and $V = CL/lambda\ z$.

Renal clearance (CL_R) was calculated by determining the total amount of drug collected in urine during the collection interval [Ae ($t1 - t2$)] divided by the area under the serum concentration-time curve for the same interval [$AUC_{t1 - t2}$]: $CL_R = Ae(t1 - t2)/AUC_{t1 - t2}$

Statistical analysis. Statistical significance was determined by using the paired t test on mean data. A P value of 0.05 or less was considered significant. All values are reported as the mean ± standard deviation.

RESULTS

Pharmacokinetic analysis was done on eight successive patients treated with foscarnet. Their mean age was 34 ± 6 years (range, 25 to 43 years), and their mean weight was 62 ± 12 kg (range, 51 to 89 kg). In six of the eight patients, estimated renal function was considered normal at the onset of the study (creatinine clearance of >1.6 ml/min per kg, ≅ 100 ml/min) while two patients had evidence of mild renal insufficiency (creatinine clearance of <1.6 ml/min per kg) (Table 1). After the administration of foscarnet, steady-state peak concentrations in plasma achieved immediately after the 2-h infusion were 306 to 876 μM on day 3 (509 ± 200) and 272 to 699 on day 14 (495 ± 149) (Table 2). Levels in plasma declined in a biexponential fashion with trough concentrations in plasma ranging from 62 to 147 on day 3 (98 ± 29) and 57 to 225 on day 14 (126 ± 59). The mean peak and trough concentrations in plasma for subjects with slightly impaired renal function did not differ significantly from the mean for all subjects and can most probably be attributed to appropriate dosage reduction. In all cases, foscarnet concentrations were below the limit detectable in plasma (33 μM) at 23 h after the last dose.

TABLE 1. Characteristics of patients treated with foscarnet

Patient no.	Age (yr)	Wt (kg)	Foscarnet dose given every 8 h (mg)[a]	Creatinine clearance (ml/min per kg)[b]	
				Day 3	Day 14
1	31	53	3,180	1.9	1.7
2	31	60	3,580	2.7	2.8
3	40	89	5,340	2.0	1.7
4	31	62	3,720	2.2	1.3
5	25	52	3,180	2.0	2.0
6	38	51	2,960	2.0	2.0
7	35	61	2,800	1.2	1.0
8	43	66	3,075	1.2	1.2
Mean	34	62	3,480	1.9	1.7
SD	6	12	811	0.5	1.6

[a] Dose based on serum creatinine on treatment day 3. Changes in renal function led to alterations in the dose administered. One milligram of foscarnet is equivalent to 3.3 μmol.

[b] Creatinine clearance was calculated from the equation of Cockcroft and Gault (2) for all patients except for patients 2 and 8, for whom it was measured as a 24-h collection.

The mean clearances in plasma on days 3 and 14 were 1.9 ± 0.6 ml/min per kg and 1.7 ± 0.9 ml/min per kg, respectively, with three of the patients showing a decrease in clearance in plasma of at least 20% (Table 3). These differences were not significant ($P = 0.37$). A significant relationship between the total plasma clearance of foscarnet and creatinine clearance was observed, but the square of the correlation coefficient of this was low ($r^2 = 0.49$). In two patients, a decrease in creatinine clearance was associated with a decline in plasma clearance of foscarnet resulting in higher plasma concentrations (Fig. 1).

The mean renal clearance on day 3 ($n = 4$) was 2.0 ± 0.9 ml/min per kg, accounting for all of the plasma clearance of foscarnet. On day 14, the renal clearance was less than the plasma clearance, being approximately 1.4 ± 0.4 ml/min per kg ($n = 2$) or 84% of the plasma clearance.

The mean half-life in plasma averaged 4.5 ± 1.2 h, determined from the last dose of therapy, while the volume

TABLE 2. Peak and trough foscarnet concentrations in serum during intermittent intravenous infusion[a]

Subject no.	Foscarnet concn (μM) at:			
	Day 3		Day 14	
	Peak	Trough	Peak	Trough
1	382	63	506	101
2	306	62	272	57
3	544	98	608	139
4	720	117	639	225
5	368	91	348	92
6	876	116	699	121
7	520	147	493	199
8	359	86	395	75
Mean	509	98	495	126
SD	200	29	149	59

[a] 60 mg/kg every 8 h, infused over 2 h (see Materials and Methods).

TABLE 3. Pharmacokinetic parameters for intravenous foscarnet given by intermittent infusion

Subject no.	Plasma clearance (ml/min per kg)		$t_{1/2}$ (h) on day 14[a]	V (liter/kg) on day 14[b]
	Day 3	Day 14		
1	2.6	1.9	3.7	0.60
2	2.9	3.6	6.6	2.00
3	1.5	1.1	3.5	0.34
4	1.3	1.1	4.9	0.45
5	2.0	1.9	5.7	0.96
6	1.5	1.5	3.4	0.44
7	1.0	0.9	5.0	0.37
8	2.0	1.7	3.3	0.49
Mean	1.9	1.7	4.5	0.74
SD	0.6	0.9	1.2	0.60

[a] $t_{1/2}$, Half-life.
[b] V, Volume of distribution.

of distribution of foscarnet averaged 0.74 ± 0.60 liter/kg for all subjects (Table 3).

DISCUSSION

This is the first study evaluating the pharmacokinetic disposition of intermittently administered foscarnet. Previous pharmacokinetic studies have been carried out only with patients receiving continuously administered intravenous foscarnet (13).

In vitro data show that most strains of cytomegalovirus are inhibited at foscarnet concentrations of 100 to 300 μM (7), while 98% of human immunodeficiency virus replication is reportedly inhibited with foscarnet concentrations of 132 μM (11). Following intermittent infusion, peak concentrations of foscarnet in plasma ranged from 272 to 876 μM in this study, above the concentrations necessary for antiviral effects. However, trough levels (57 to 225 μM) did fall below these concentrations. In addition, Sjovall et al. (13) reported concentrations in cerebrospinal fluid averaging 43 ± 19% of simultaneously measured concentrations in plasma in five patients. However, since four of these subjects had evidence of inflamed meninges, further investigation of cerebrospinal fluid and intravitreal penetration must be carried out to determine whether adequate levels are achieved in these tissues.

Sjovall et al. (13) observed a half-life in plasma of 3.3 h, using a two-compartment model after continuous intravenous infusion. This half-life is slightly shorter than our mean of 4.5 h. In addition, the mean clearance in plasma was 214 ml/min per 1.73 m^2 (13), while the clearance in plasma for our patients, corrected for body surface area, was considerably lower, averaging 106 and 101 ml/min per 1.73 m^2 on days 3 and 14, respectively. The differences in the pharmacokinetic parameters between these studies may be due to a number of factors. First, the patients enrolled in the previous study were asymptomatic for human immunodeficiency virus infection except for lymphadenopathy, while our patients had severe complications of infection, such as cyto-

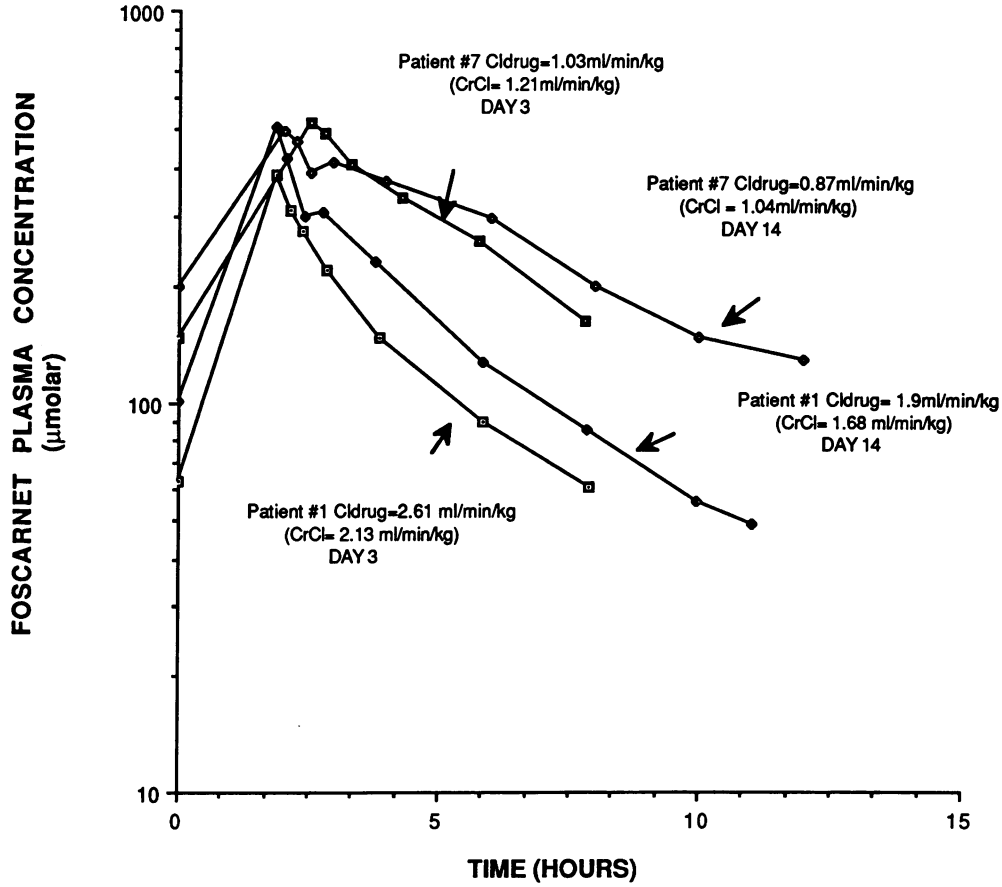

FIG. 1. Foscarnet concentrations in plasma versus time for two patients (patients 1 and 7) with changing renal function on days 3 and 14.

megalovirus retinitis, and had poor nutritional status. Second, the study designs differed; Sjovall et al. administered large daily doses of foscarnet via continuous intravenous infusion, whereas we administered only 17 to 33% of this total daily dose intermittently. In addition, sample collection in the earlier work was carried out for only 6 h, less than 2 half-lives post-drug administration compared with 23 h postinfusion in our study. Finally, the large variability in plasma levels measured by Sjovall et al. made curve fitting difficult.

Our data support previous work showing that the kidney is important in the excretion of foscarnet with no known metabolites (13). The renal clearance is approximately 80% of the plasma clearance. On the basis of this information, dosage modifications are necessary in patients with decreased renal function.

In this study, two subjects developed mild renal impairment during the course of therapy, and this may be attributed to the nephrotoxicity of the agent (1; J. Sjovall, Astra Alab, unpublished data). We found that these patients had a larger area under the curve on day 14 (adjusted for dose) compared with that of patients with stable renal function. We experienced a much lower incidence of declining renal function than that reported previously in studies of continuously administered foscarnet in which up to 20% of the patients had elevations in serum creatinine (2 to 3.5 times the base line) after 7 to 21 days of therapy. This may be partially explained by the larger total daily doses administered by continuous infusion (10, 14).

In summary, the results of this investigation show that the intermittent administration of foscarnet leads to plasma concentrations above those necessary to inhibit human herpesviruses and the human immunodeficiency virus and is associated with a low incidence of renal toxicity. In addition, this mode of administration is more practical and less costly than continuous infusion, allowing for self-administration in an outpatient setting.

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