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Penetration of Foscarnet into Cerebrospinal Fluid of AIDS Patients

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The diffusion of foscarnet into cerebrospinal fluid (CSF) was studied in 27 patients with AIDS. Foscarnet was administered intravenously at various dosages at 12-h intervals. Concentrations in plasma and CSF at the end of foscarnet infusion or 1, 3, 5, 6, and 12 h after infusion were determined by high-performance liquid chromatography. Thirty-seven samples were obtained. The median concentration of foscarnet in CSF was 80 μmol/liter (range, 0 to 500 μmol/liter). The CSF foscarnet concentration was greater than the 50% inhibitory concentration for human immunodeficiency virus type 1 and was equal to or greater than the 50% inhibitory concentration for cytomegalovirus in most cases. The penetration of foscarnet into CSF, as expressed by the ratio of the concentration in CSF to the simultaneous concentration in plasma, ranged from 0 to 3.4 (median, 0.27) and was highly correlated with the presence of cells within CSF and the length of foscarnet therapy. Good diffusion of foscarnet in CSF allows evaluation of this drug in central nervous system cytomegalovirus and human immunodeficiency virus infections in patients with AIDS.

Foscarnet is an antiviral drug that is active in vitro against a wide range of viruses including cytomegalovirus (CMV), herpes simplex virus, and human immunodeficiency virus (HIV) (3, 7, 10). Recent studies have demonstrated the clinical activity of foscarnet in severe CMV infections in patients with AIDS. In CMV retinitis, foscarnet provided improvement similar to that of ganciclovir, but survival was significantly longer than that with foscarnet. This may have been due to the anti-HIV activity and/or synergistic anti-HIV activity of foscarnet-nucleoside analog combinations (5, 13).

The pharmacokinetic parameters of foscarnet established after either continuous or intermittent intravenous infusion, i.e., every 8 or 12 h, appear very similar in terms of clearance and volume of distribution (2, 12, 14). At physiologic pH, foscarnet is highly ionized, with protein binding of 15% and limited cell penetration. Penetration of foscarnet into cerebrospinal fluid (CSF) has previously been studied in only a few patients with asymptomatic HIV infection, with levels ranging from 13 to 68% of the simultaneous concentration in plasma (12). The aim of the study described here was to evaluate the penetration of foscarnet into the CSF of patients with AIDS.

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MATERIALS AND METHODS

Patients. A total of 27 hospitalized AIDS patients entered the study (23 male; 4 female; mean age, 34 ± 7.5 years; age range, 21 to 49 years). Informed consent was obtained from each patient or from his or her family. Median CD4 lymphocyte cell counts were 21/ml^3 (range, 2 to 510/ml^3). All patients had AIDS according to the revised classification of the Centers for Disease Control and Prevention. The indication for foscarnet therapy was CMV infection in 18 patients (retinitis, n = 7; colitis, n = 3; encephalitis, n = 4; peripheral neuropathy, n = 1; pneumonitis, n = 1; disseminated infection, n = 2) and HIV encephalitis in 5 patients. In the other four patients, only one dose of foscarnet was administered for the purpose of the present study, a lumbar puncture being indicated because of diagnostic workup for central nervous system diseases (lymphoma, n = 3; toxoplasmosis, n = 1). All patients had normal serum creatinine levels at the time of foscarnet concentration measurement (mean, 66.5 ± 17.5 μmol/liter).

Dosage and sampling. Foscarnet was administered through a central vein in 24 of 27 patients and through a peripheral vein in the 3 remaining patients. The dosage ranged from 56 to 213 mg/kg of body weight (median, 100 mg/kg) over 2 to 6 h (median, 3 h), depending on the patient's clinical status and the indication (induction or maintenance therapy) for foscarnet. In 27 patients, the duration of infusion was 2 to 3 h, whereas in the 10 others it was 5 to 6 h. During each foscarnet infusion, all patients were hydrated with 500 to 1,000 ml of saline solution. In some patients, the highest doses (180 to 213 mg/kg) were administered as a loading dose for the first infusion.

A total of 37 CSF samples were drawn from the 27 patients. CSF samples were obtained immediately (n = 18) or at 1 h (n = 2), 3 h (n = 10), 5 h (n = 1), 6 h (n = 5), or 12 h (n = 1) after the end of the foscarnet infusion. Seventeen of the 37 samples were drawn after the first dose of foscarnet, whereas the other 20 CSF samples were obtained after several days of foscarnet therapy (2 to 36 days; median, 8 days). Blood was sampled at the time that CSF was drawn and from some patients at various times before infusion (trough level), at the end of infusion (peak level), and after the end of infusion.

CSF samples were used to determine CSF characteristics, for microbiological purposes, and to assay for foscarnet. Meningeal inflammation was defined as the presence of any

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TABLE 1. CSF foscarnet concentrations and CSF/plasma ratio by time of CSF sampling

Time of sampling after end of infusion (h)	Foscarnet concn in CSF (μmol/liter [range]) for the following foscarnet dosage[a]:			Foscarnet CSF/plasma ratio (range) (n = 37)[a]
	56 mg/kg (n = 1)	80–105 mg/kg (n = 23)	160–210 mg/kg (n = 13)	
0	53	30 (0–127) (n = 13)	216 (70–500) (n = 4)	0.135 (0–1.51)
1 (n = 2)	ND[b]	176 (200)	ND	0.36 (0.77)
3	ND	80 (23–193) (n = 5)	83 (57–160) (n = 5)	0.31 (0.14–0.94)
5	ND	57 (n = 1)	ND	0.33
6	ND	233 (n = 1)	98 (87–113) (n = 4)	0.69 (0.25–1.15)
12	ND	57 (n = 1)	ND	3.4

[a] Data are median values (ranges).
[b] ND, not done.

leukocytes in the CSF. Plasma and CSF were stored at −70°C until they were analyzed.

Assay procedure. Foscarnet concentrations in plasma and CSF were determined by a reversed-phase high-performance liquid chromatography assay with electrochemical detection by a previously described method (8, 14). Plasma and CSF samples were injected directly onto the column after dilution and ultrafiltration. The assay sensitivity limit was 15 μmol/liter. Interday coefficients of variation were 10 and 8%, respectively, for plasma samples spiked with 133 and 417 μmol of foscarnet per liter.

Statistical analysis. Because of very wide standard deviations, results are given as medians and ranges. The Wilcoxon-Mann-Whitney test was used for comparison of data between groups. Multivariate analysis by forward stepwise logistic regression with the BP.STAT module (9) was done to examine the relationships of variables to penetration of foscarnet into CSF.

RESULTS

None of the lumbar punctures was traumatic, and in fact, none of the 37 CSF samples contained any erythrocytes. For most patients there were no leukocytes in the CSF, and only 11 samples contained 2 or more leukocytes per cubic milliliter of CSF (median, 10.5; range, 2 to 88).

The median concentration of foscarnet in CSF was 80 μmol/liter (range, 0 to 500 μmol/liter). In 27 of the 37 CSF samples (73%), the concentration of foscarnet was within the range of in vitro CMV virostatic concentrations, i.e., >50 μmol/liter. The median percentage of penetration, expressed as the ratio of the concentration in CSF to the simultaneous level in plasma, was 27% and ranged from 0 to 340%. Foscarnet concentrations in CSF and the CSF/plasma ratio according to the time of sampling after the end of foscarnet infusion are given in Table 1. There was a wide range of variation in the CSF foscarnet concentration which was apparently unrelated to the foscarnet dosage or the time of sampling after infusion. The CSF/plasma ratio was somewhat higher in cases of delayed CSF sampling (median ratio, 0.135 at time zero [n = 18], 0.31 at 3 h [n = 10], and 0.69 at 6 h [n = 5]), although it was not significant by regression analysis (r = 0.19).

Univariate analysis showed that the amount of foscarnet in CSF was highly correlated with inflammation of the meninges (P = 0.002) and that the percentage of foscarnet penetration into CSF was also correlated with the time of sampling after the end of infusion (P = 0.004). The concentration of foscarnet in CSF was not correlated to the dose or to the concentration in plasma (Fig. 1). For the same infusion dose, CSF foscarnet levels and the CSF/plasma ratio were more than twice as high in patients with inflamed meninges as in patients with normal CSF, the difference being highly significant (Table 2). This appeared even more evident when only samples taken at the end of foscarnet infusion, i.e., at the time of peak levels in plasma, were considered. Foscarnet concentrations appeared to be sustained in the CSF, remaining stable whatever the time point of sampling (0 to 12 h) after the end of infusion (Fig. 2).

Multivariate stepwise analysis indicated that the variables strongly and independently associated with CSF foscarnet concentrations were, in decreasing order of usefulness, cells in CSF (r = 0.512; P = 0.002), length of infusion (r = 0.458; P = 0.005), and protein concentration in CSF (r = 0.481; P = 0.003). For the CSF/plasma ratio, the relative contribution of the variables was, by rank of importance, CSF cells (r = 0.473; P = 0.004), time of CSF sampling after the end of infusion (r = 0.352; P = 0.031), and duration of foscarnet therapy (r = 0.37; P = 0.025).

DISCUSSION

In the present study, foscarnet appeared to penetrate into the CSF of patients with AIDS. The median percentage of penetration at the time of the peak level in plasma was 13.5%. In patients with a meningeal barrier defect, as assessed by the presence of cells within CSF, the diffusion of foscarnet was four times as high as that in patients with normal CSF. The distribution of foscarnet in CSF was previously studied in five patients with asymptomatic HIV infection during a continuous intravenous infusion (12). The concentration in their CSF ranged from 47 to 80 μmol/liter, and the CSF/plasma concentration ratio ranged from 0.13 to 0.68 (mean, 0.43 ± 0.19). The somewhat higher CSF foscar-

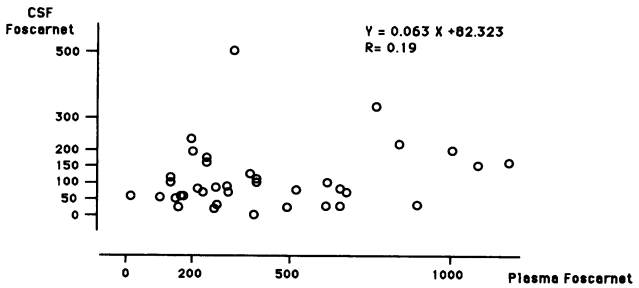

FIG. 1. Foscarnet concentration in CSF versus the simultaneous concentration in plasma (both in micromoles per liter). The data represent 37 samples from 27 patients. Regression analysis shows the absence of a correlation.

TABLE 2. Foscarnet penetration into CSF according to CSF cells

Sample	Foscarnet dosage (mg/kg)[a]	No. of samples	Concn (μmol/liter) in CSF	CSF/plasma ratio
All samples				
Cells in CSF				
Absent	126.04 ± 45.31	25	70[b]	0.21[c]
Present	125.33 ± 46.91	12	160[b]	0.465[c]
Sampling at end of intravenous infusion				
Cells in CSF				
Absent	107.8 ± 31	13	67[d]	0.11[e]
Present	120.8 ± 56.2	5	110[d]	0.43[e]

[a] Foscarnet dosage data are means ± standard errors of the means. CSF and CSF/plasma ratio data are medians. Comparison of data was done by the Wilcoxon-Mann-Whitney test.
[b] $P = 0.005$.
[c] $P = 0.058$.
[d] $P = 0.011$.
[e] $P = 0.055$.

net concentrations found in some of the patients in our study could have been due to the different populations studied as well as to the presence of meningeal inflammation in some of these patients. It is noteworthy that interindividual variations in CSF foscarnet concentrations were high, ranging from 0 to 500 μmol/liter. In only one sample was foscarnet undetectable in CSF. This could be due to early CSF sampling or a level below the lower limit of detection (15 μmol/liter). High variability has already been observed during pharmacokinetic studies of foscarnet in plasma (6, 14). The percentage of penetration of foscarnet into CSF appeared to increase with a longer delay between the end of infusion and CSF sampling; the median CSF/plasma ratio was 0.33 in samples taken from 1 to 12 h after the end of infusion versus 0.135 in samples taken at the time of the peak level in plasma. This suggests that foscarnet diffusion into CSF is a slow process. Although the method used to study foscarnet penetration into CSF was suboptimal because the concentration at only a single time point after an infusion was determined, it gives useful information about the range

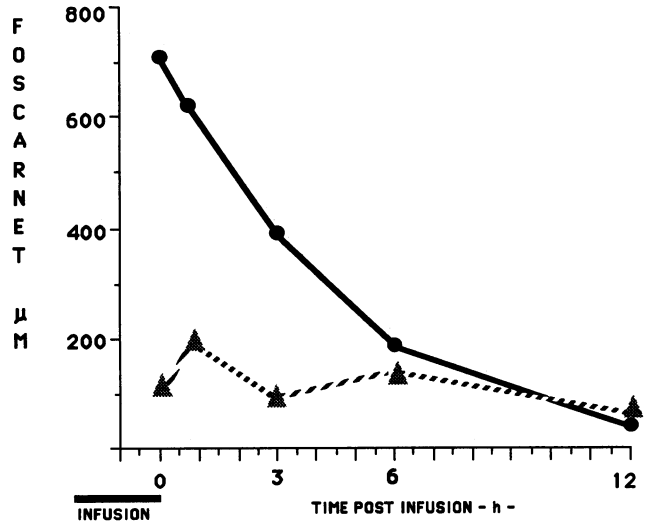

FIG. 2. Foscarnet concentrations in plasma (●) and CSF (▲) were determined at various times after the end of an infusion of foscarnet; samples were taken at the end of infusion (time zero; $n = 18$) or after 1 h ($n = 2$), 3 h ($n = 10$), 6 h ($n = 5$), or 12 h ($n = 1$). Each point represents the mean.

of concentrations that can be achieved in CSF with standard foscarnet treatment. Measurement of foscarnet concentrations in CSF and plasma at multiple time points after administration of a bolus dose and comparison of the areas under the concentration-time curves would have been more accurate but they would have been inapplicable. Continuous infusion would have been more appropriate for simultaneously measuring concentrations of foscarnet in CSF and plasma at steady state. However, because of the severe clinical status of the patients, we had to take into account the foscarnet administration scheme as well as the date that the lumbar puncture had to be performed, which were determined according to each patient's clinical situation.

Although no accumulation of foscarnet occurred in plasma with intermittent infusion every 8 or 12 h because of the short half-life of foscarnet in plasma (14), it is interesting that CSF foscarnet concentrations remained almost the same during the 6 to 12 h postinfusion. CSF foscarnet concentrations were within the range of antiviral activity, exceeding the 50% inhibitory concentration for HIV (25 μmol/liter) in 90% of samples, and in most cases they were within the range of the 50% inhibitory concentrations for CMV (50 to 200 μmol/liter) (1, 11, 15).

Although foscarnet achieves concentrations in CSF that seem sufficient for inhibition of CMV replication, it is not known what amount of foscarnet reaches the site of infection in the brain or infected cells. Still, although there is no evidence to correlate drug activity against CMV infection in the central nervous system with the drug concentrations measured in CSF, it is noteworthy that the four patients with CMV encephalitis showed dramatic improvement with foscarnet therapy (range of CSF foscarnet concentration, 80 to 500 μmol/liter).

Multivariate analysis showed that inflammation of the meninges was the most important factor contributing to foscarnet penetration into the CSF and that a longer infusion time for a given dose allowed better distribution into the CSF. It is not possible to determine whether continuous infusion over 24 h would allow an even better foscarnet distribution into the CSF, but a previous study (12) suggests that this is not the case. Although the exact mechanism of foscarnet distribution in CSF could not be determined by our study, the correlation of CSF foscarnet levels with CSF inflammation (cells and protein) suggests a passive mechanism. Conversely, the increase in the concentration of foscarnet in CSF with a longer duration of infusion could be

attributed to an active saturable diffusion process, although it could also be due to a slow diffusion process through the blood-brain barrier. We can only emphasize that with a twice-daily regimen of foscarnet, as is now usually recommended, CSF foscarnet concentrations were very stable over time.

On the basis of these results, clinical studies of treatment with foscarnet for central nervous system diseases caused by CMV that occur in patients with AIDS are warranted. The potential usefulness of foscarnet in combination with zidovudine or didanosine should also be considered for the treatment of HIV encephalitis because of the synergistic activity between foscarnet and nucleoside analogs (4, 5) and the penetration of foscarnet into the CSF.

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