ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1010–1014
0066-4804/93/051010-05$02.00/0

Vol. 37, No. 5

Foscarnet Penetrates the Blood-Brain Barrier: Rationale for Therapy of Cytomegalovirus Encephalitis

U. R. HENGGE,[1]†* N. H. BROCKMEYER,[1] R. MALESSA,[2] U. RAVENS,[3] AND M. GOOS[1]

Department of Dermatology, Allergy and Venerology,[1] Department of Neurology,[2] and Department of Pharmacology,[3] University of Essen, W-4300 Essen, Germany

Received 5 October 1992/Accepted 7 March 1993

Foscarnet (phosphonoformate) is a potent virustatic drug against herpes-like viruses and is widely used in the therapy of cytomegalovirus infections in immunosuppressed patients. To obtain data on its penetration across the blood-brain barrier, we determined concentrations of foscarnet in cerebrospinal fluid and in plasma specimens from 26 patients with human immunodeficiency virus (stages 2 to 6 by Walter Reed Army Institute of Research classification) after a single infusion of 90 mg of foscarnet per kg of body weight and at steady state by electrochemical detection by high-pressure liquid chromatography. Penetration coefficients were correlated with the integrity of the blood-brain barrier. After a single infusion of foscarnet, levels in plasma ranged from 297 to 1,775 μg/ml (990 to 5,920 μmol/liter), with a mean of 766 ± 400 μg/ml. Corresponding levels in cerebrospinal fluid were 57 to 225 μg/ml (190 to 750 μmol/liter), with a mean of 131 ± 52 μg/ml. The penetration coefficient was 0.05 to 0.72 (mean, 0.23 ± 0.16). At steady state, mean foscarnet levels in plasma were 464 ± 219 μg/ml (1,553 μmol/liter) and mean levels in cerebrospinal fluid were 308 ± 155 μg/ml (1,023 μmol/liter). The penetration coefficient was 0.66 ± 0.11. Although penetration coefficients were highly variable after a single administration and at steady state, the concentrations of foscarnet attained in cerebrospinal fluid are sufficient for complete inhibition of cytomegalovirus replication in vitro. In conclusion, we show that foscarnet seems to be the drug of choice for the treatment of cytomegalovirus encephalitis, because it penetrates the blood-brain barrier and is found in the cerebrospinal fluid in virustatic concentrations. Foscarnet might be considered for additive therapy for human immunodeficiency virus encephalitis in combination with zidovudine or dideoxyinosine.

Cytomegalovirus infection is the most common opportunistic infection occurring late during the course of human immunodeficiency virus (HIV) disease and causing high mortality (33). Besides retinitis, colitis, pneumonitis, and ulcers (3), infections of the central nervous system (CNS) by cytomegalovirus (CMV) are increasingly recognized and show a broad variety of neurologic symptoms and neuropathologic findings.

Postmortem investigations revealed CNS involvement in about 20% of patients with HIV (20) and showed cells with CMV inclusions in 80% of these patients (31). Histologically, CMV meningoencephalitis may present as microglial nodules (22, 25, 31), necrosis of parenchyma (31), and hemorrhagic vasculitis (16). Spinal cord involvement may manifest as necrotizing myelopathy with perifocal demyelination (31) or as meningoradiculitis with vascular involvement (2, 8, 31), both causing ascending paralysis and loss of sensitivity. CMV infection may also present as acute cauda equina syndrome, with incontinence (23). Cytologically, CMV can infect all cells in the CNS (astrocytes, neurons, oligodendroglia [22, 28]) as well as monocytes, lymphocytes (28), and capillary endothelia (22, 28). Thus, infection of endothelia seems to be the portal of entry into the CNS, and CMV might be spread subsequently from the choroid plexus via the cerebrospinal fluid (CSF).

Foscarnet (=phosphonoformate; Foscavir; Astra, Södertälje, Sweden) is a potent virustatic drug against herpes-like viruses (e.g., CMV, herpes simplex virus, and Epstein-Barr virus) which has been shown to prolong survival in patients with CMV retinitis, in contrast to ganciclovir (1). Since foscarnet also inhibits the reverse transcriptase of HIV, p24 antigen was found to decrease significantly under foscarnet therapy in both in vitro (32) and in vivo (15) studies.

In the present investigation, we measured the penetration of foscarnet across the blood-brain barrier by estimating the concentrations of foscarnet in CSF and in plasma specimens from 26 patients with HIV at stages 2 to 6 according to Walter Reed Army Institute of Research (WR) classification. The concentrations were determined 1 h after a single administration (90 mg/kg of body weight) and under steady-state conditions (90 mg/kg of body weight twice a day [b.i.d.] for at least 4 weeks).

MATERIALS AND METHODS

Patients. Twenty-six patients with HIV (22 male homosexuals, 2 male intravenous drug abusers, 1 African woman, and 1 female transfusion recipient; WR stages 2 to 6) between 27 and 56 years old underwent lumbar puncture for different neurologic reasons; the patients' characteristics are listed in Table 1. Informed written consent was obtained from all patients.

Study design. The patients received 90 mg of foscarnet per kg of body weight over a 2-h infusion period via a central venous catheter and an infusion pump; exactly 1 h after the end of administration of foscarnet, lumbar puncture was performed and peripheral blood was drawn. The same

* Corresponding author.
† Present address: Dermatology Branch, National Cancer Institute, Building 10, 12N260, 9000 Rockville Pike, Bethesda, MD 20892.

TABLE 1. Patients' characteristics[a]

Patient no.	Reason for lumbar puncture	WR stage	CDC[b] stage	$CD4^+$ lymphocytes/μl in plasma	β_2 microglobulin in plasma (mg/liter)
1	HIV/CMV encephalitis	6	IV A, B, C1, C2, D	16	5.3
2	S.o.[c] neurosyphilis	3	III A	450	2.6
3	Headache	4	IV A	250	5.7
4	S.o. neurosyphilis	4	IV A	275	3.0
5	Toxoplasmosis	6	IV A, B, C1, C2, D	24	4.0
6	Headache	3	III A	590	1.8
7	Unconsciousness	6	IV A, B, C1, C2		2.7
8	Hemiparesis	5	IV A, C2	220	3.4
9	S.o. neurosyphilis	2	II	950	2.5
10	S.o. neurosyphilis	4	IV A, B	271	3.0
11	HSV[d] encephalitis	5	IV A, B, C2	180	5.3
12	S.o. neurosyphilis	4	III A	367	4.4
13	Dementia, posttoxoplasmosis	6	IV A, B, C1, C2	10	4.8
14	S.o. neurosyphilis	3	III A	577	2.9
15	Seizure	6	IV A, C1, D	22	4.4
16	Brainstem Seizure	6	IV A, C1, E	80	5.3
17	S.o. HIV encephalitis and S.o. neurosyphilis	3	III B	419	5.3
18	S.o. toxoplasmosis/extrapulmonary tuberculosis	5	IV A	133	4.9
19	Seizure	3	III A	450	4.0
20	Cryptococcosis	6	IV A, B, C1	11	4.9
21	Cryptococcosis	6	IV A, B, C1, D	8	3.5
22	Ascending paralysis, palsy of cranial nerves	6	IV A, B, C1	15	4.8
23	HIV/CMV encephalitis	6	IV A, B, C1, C2	10	4.9
24	CMV encephalitis	6	IV A, B, C1, D	4	4.2
25	Dementia	6	IV A, B, C1	2	4.5
26	S.o. CMV encephalitis, headache	6	IV A, B, C1, C2, D	5	4.7

[a] Patients 1 to 21 received a single infusion (90 mg/kg of body weight), and treatment of patients 22 to 26 represents steady state (90 mg/kg of body weight b.i.d. for at least 4 weeks).
[b] CDC, Centers for Disease Control.
[c] S.o., suspicion of.
[d] HSV, herpes simplex virus.

procedure was performed with five patients who received foscarnet (90 mg/kg of body weight b.i.d. for at least 4 weeks) for CMV infection. The treatment of these patients represents steady-state conditions.

Statistical analysis. All results are shown as means ± standard deviations of duplicate tests. Statistical calculations were done by the χ^2 test.

Assay method. The determination of foscarnet concentrations was modified according to reference 26.

After centrifugation, plasma and CSF samples were stored at −80°C until analysis. The samples were heated at 56°C for 30 min before centrifugation at 2,000 × *g* for 10 min. Subsequently, ultrafiltration was performed in a Centricon 30 tube (Amicon, Denver, Colo.) at 1,500 × *g* for 10 min. Under these conditions, foscarnet was stable (4). Recovery of foscarnet after ultrafiltration was >98.5%.

Each sample was analyzed as duplicates at 1:1 and diluted by 1:10 and 1:100 with mobile-phase buffer (25:75 [vol/vol] methanol-phosphate, pH 5.8; 1 mM tetraethylammonium hydrogen sulfate; 0.2 mM sodium PP_i). Phenol was used as an internal standard. All chemicals used were of analytical purity grade and were obtained from Merck, Darmstadt, Germany.

The analytical column (inside diameter, 125 by 4 mm) was a Hibar Pre-Packed Column RT (LiChrosorb RP-18) with 5-μm particles. It was operated at an ambient temperature, with a typical back pressure of 3,200 lb/in^2.

The liquid chromatograph consisted of an solvent delivery system (SP 8810; Spectra Physics, San Jose, Calif.), an autosampler (SP 8775; Spectra Physics), and an electrochemical detector (641 VA-detector; Metroohm, Böblingen, Germany) with a guard cell and an analytical cell. The potential on the analytical cell was set at +1.25 V, and the current was 100 nA. The signal from the analytical cell was monitored with a computing integrator (SP 4290; Spectra Physics).

Quantification was based on measuring standard solutions of foscarnet in mobile-phase buffer. The volume injected was 50 μl. The flow rate was 1.0 ml/min. Linear calibration was obtained between 12 and 770 μM in the injected volumes. Control samples with known concentrations of foscarnet, which underwent the same preparation, were injected after seven test vials were used to check the performance of the analytical system. The interday variation coefficient was 11%.

Quality of the blood-brain barrier. The quality of the blood-brain barrier was assessed by the CSF/plasma ratio for albumin × 1,000 (normal value, <7.4). The higher the ratio was, the more severe the disturbance of the blood-brain barrier was. Local immunoglobulin G (IgG) production was assessed by the IgG index by the method of Delpech and Lichtblau (7); the CSF/plasma ratio for IgG was also determined. Specific IgG directed against *Treponema pallidum* (hemagglutination assay) (TPHA) and HIV was calculated by *T. pallidum* IgG antibodies in CSF/total IgG in CSF divided by $TPHA_{plasma}/IgG_{plasma}$. Normal ranges in CSF

TABLE 2. Concentrations of foscarnet in plasma and CSF after a single-dose administration of 90 mg/kg of body weight

Patient no.	Foscarnet concn[a] (μg/ml) in:		Q_{fos}[b]
	Plasma	CSF	
1	400 ± 27	156 ± 8	0.39
2	1,150 ± 41	81 ± 6	0.07
3	297 ± 15	95 ± 9	0.32
4	1,550 ± 80	114 ± 10	0.07
5	1,019 ± 40	83 ± 3	0.08
6	713 ± 30	213 ± 12	0.30
7	532 ± 20	133 ± 10	0.25
8	953 ± 23	88 ± 8	0.09
9	665 ± 25	94 ± 8	0.14
10	1,025 ± 37	85 ± 6	0.08
11	688 ± 98	190 ± 20	0.28
12	1,775 ± 74	87 ± 9	0.05
13	311 ± 29	225 ± 11	0.72
14	443 ± 10	105 ± 6	0.23
15	422 ± 19	122 ± 10	0.29
16	1,184 ± 40	224 ± 12	0.19
17	957 ± 31	123 ± 6	0.13
18	556 ± 18	211 ± 10	0.38
19	688 ± 63	57 ± 8	0.08
20	324 ± 12	100 ± 8	0.31
21	449 ± 27	166 ± 10	0.37

[a] Results are shown as means ± standard deviations of duplicate tests for each 1:1, 1:10, and 1:100 dilution.
[b] Q_{fos}, CSF/plasma ratio for foscarnet.

were as follows: protein, 15 to 45 mg/dl; CSF/plasma ratio for albumin, <7.4; CSF/plasma ratio for IgG, <4.2; CSF/plasma ratio for specific activity against TPHA, ≤1.0; CSF/plasma ratio for specific activity against HIV, ≤2.0.

RESULTS

Foscarnet concentrations in plasma and CSF after a single-dose administration of 90 mg/kg of body weight are shown in Table 2. Levels in plasma ranged from 297 to 1,775 μg/ml (990 to 5,920 μmol/liter), with a mean of 766 ± 400 μg/ml (2,587 μmol/liter). Corresponding levels in CSF were 57 to 225 μg/ml (190 to 750 μmol/liter), with a mean of 131 ± 52 μg/ml (437 μmol/liter). The penetration coefficient was 0.05 to 0.72, with a mean of 0.23 ± 0.16.

Under steady-state conditions (4 weeks of therapy with 90 mg/kg of body weight b.i.d.), concentrations were as shown in Table 3. Mean foscarnet levels in plasma were 464 ± 219 μg/ml (1,553 μmol/liter), and mean levels in CSF were 308 ± 155 μg/ml (1,023 μmol/liter). The penetration coefficient was 0.66 ± 0.11. Two of three patients (23 and 24) with CMV encephalitis, confirmed by polymerase chain reaction, experienced remarkable clinical improvement after 4 and 2.5 weeks of treatment with foscarnet. Patient 23 showed enhanced vigilance and improved paralysis of the lower extremities and he regained the ability to walk. He died from sepsis 5.5 months after the initiation of foscarnet treatment. Patient 24 died 3 months later from respiratory distress due to pulmonary Kaposi's sarcoma and staphylococcal pneumonia.

TABLE 3. Concentrations of foscarnet in plasma and CSF at steady state

Patient no.	Foscarnet concn[a] (μg/ml) in:		Q_{fos}[b]
	Plasma	CSF	
22	634 ± 29	437 ± 17	0.69
23	219 ± 24	175 ± 19	0.80
24	567 ± 28	322 ± 14	0.56
25	183 ± 16	98 ± 8	0.54
26	715 ± 19	511 ± 14	0.71

[a] Results are shown as means ± standard deviations of duplicate tests for each 1:1, 1:10, and 1:100 dilution.
[b] Q_{fos}, CSF/plasma ratio for foscarnet.

Results of CSF examination for cells, protein concentration, and CSF/plasma ratio for albumin, IgG, and specific IgG against TPHA and HIV are shown in Table 4. Seven of 26 (27%) patients had disturbance of the blood-brain barrier. Intrathecal IgG synthesis was detected in 14 of 26 (54%) patients. The concentration of foscarnet in CSF correlated with the WR stage ($P < 0.05$). No correlation between foscarnet levels in plasma or CSF and cell count, protein content, CSF/plasma ratio for IgG or albumin, or the specific activity of antibodies against TPHA and HIV was found (each $P > 0.05$).

DISCUSSION

Because of the increasing importance of CMV infection in patients with HIV (20, 24, 27) extended pharmacokinetic data on foscarnet are needed. Foscarnet is a very small and highly negatively charged molecule (4) which is not bound to proteins in plasma. Its penetration into CSF is thought to occur by passive diffusion. Because of foscarnet's first half-life of 1.5 h (29), drawing of samples 1 h after the end of administration was considered to be sufficient for adequate penetration into the CSF. As a limitation of our study, we were not able to administer foscarnet continuously for patients' convenience. For obvious reasons, we could obtain CSF only at the time when lumbar puncture was performed, except for with one patient who had a temporary shunt. According to the literature, peak concentrations in plasma were determined to be 450 to 550 μmol/liter for six patients after infusion of 90 mg/kg of body weight b.i.d. for 2 weeks (34). Fanning et al. (10) found levels in plasma from 243 to 654 μmol/liter (mean, 486 μmol/liter) after administration of 90 mg/kg of body weight per day. Mean steady-state concentrations in plasma were 228 μmol/liter (164 to 529 μmol/liter) in 13 patients (29) and 261 μmol/liter (115 to 741 μmol/liter) in 14 patients after 6 to 21 days of continuous infusion (0.09 to 0.19 mg/kg/min = 130 to 274 mg/kg daily) of foscarnet (12). Pharmacokinetic data for 11 patients after twice-daily administrations of foscarnet (90 mg/kg of body weight for 2 weeks) were recently evaluated by Taburet et al. (30). In our study, levels in plasma after infusion of 90 mg/kg of body weight showed a high interindividual variability (990 to 5,920 μmol/liter). This may be due to differences in distribution of foscarnet into body compartments or to differences in excretion by the kidneys since drug administration and sampling were constant. Deposition in the bone, which can involve up to 20% of the foscarnet administered, may also cause variation in foscarnet concentrations (4). Concentrations in plasma under steady-state conditions in our investigation were also highly variable but were always above the concentrations that were virustatic in vitro (29, 33).

Foscarnet concentrations in CSF were 47 to 80 μmol/liter (mean, 68.5 μmol/liter) for five healthy HIV-positive patients (WR stages 2 to 3) without HIV-related symptoms after continuous infusion of 0.14 to 0.19 mg/kg of body weight over 24 h (=202 to 274 mg/kg daily) for 2 to 21 days (29);

TABLE 4. Analysis of CSF

Patient no.	Cells/mm^3	Protein[a] (mg/dl)	$Q_{albumin}$[b]	Q_{IgG}[c]	Q_{sTPHA}[d]	Q_{sHIV}[e]	Quality of blood-brain barrier[f]
1	3	112	24.9	18.2	ND[g]	11.6	+
2	36	41	5.0	3.8	0.5	1.2	−
3	4	53	4.7	4.2	0	12.4	−
4	10	53	6.1	6.5	0.5	5.0	−
5	0	34	5.6	4.1	0	2.9	−
6	40	35	4.4	3.6	10.0	3.2	−
7	0	26	4.6	4.2	0.2	25.6	−
8	0	75	12.2	8.1	0	ND	+
9	62	62	6.6	6.2	0.5	0.1	−
10	42	25	2.8	2.0	8.0	0.1	−
11	18	37	3.6	2.1	0	7.0	−
12	ND	25	3.5	1.8	4.0	3.8	−
13	26	45	7.0	4.0	0	21.6	−
14	99	66	24.5	5.9	0	3.4	+
15	1	58	9.5	6.3	0	4.1	+
16	1	34	7.7	5.6	0	3.3	+
17	15	53	6.8	4.8	1.0	ND	−
18	79	41	4.8	4.6	0	ND	−
19	4	59	5.0	21.0	0.2	16.1	−
20	14	75	7.2	6.2	0	1.7	−
21	5	42	5.8	3.0	0	2.5	−
22	40	364	68.1	63.0[h]	0	0.8	+
23	19	30	6.4	4.0	0.4	6.6	−
24	15	36	6.4	3.9	0	3.9	−
25	23	87	8.9	7.6	0.1	16.8	+
26	21	47	6.0	8.9	0	10.7	−

[a] Normal range, 15 to 45 mg/dl.
[b] $Q_{albumin}$, CSF/plasma ratio for albumin. Normal range, <7.4.
[c] Q_{IgG}, CSF/plasma ratio for IgG. Normal range, <4.2.
[d] Q_{sTPHA}, CSF/plasma ratio for specific activity against TPHA. Normal range, ≤1.0.
[e] Q_{sHIV}, CSF/plasma ratio for specific activity against HIV. Normal range, ≤2.0.
[f] The quality of the blood-brain barrier was assessed by the CSF/plasma ratio for albumin. − and + indicate integrity and nonintegrity of the blood-brain barrier, respectively.
[g] ND, not determined.
[h] IgG in CSF was 98.6 mg/dl (normal range, 1 to 2.8 mg/dl) in a patient with ascending paralysis and central nervous palsy suggesting humoral pathogenesis.

corresponding concentrations in plasma ranged from 113 to 477 μmol/liter. The CSF/plasma ratio was 0.13 to 0.68 (mean, 0.43). Besides these five case reports, no data on foscarnet penetration into CSF are available. In our study with 26 patients at various stages according to the WR classification, levels in CSF ranged from 57 to 225 μg/ml (190 to 750 μmol/liter; mean, 131 μg/ml) after a single-dose administration of foscarnet; the penetration coefficient after a single-dose administration was 0.05 to 0.72 (mean, 0.23 ± 0.16). At steady state, foscarnet concentrations in CSF were 308 μg/ml and concentrations in plasma were 464 μg/ml (1,143 and 1,557 μmol/liter, respectively); the penetration coefficient at steady state was 0.54 to 0.80 (mean, 0.66 ± 0.11). The penetration of foscarnet into CSF was confirmed by the clinical observation of headache, paresthesia, restlessness (9), and seizures after twice-daily infusions of foscarnet for maintenance therapy. In contrast to the patients studied by Sjövall et al. (29), we were not able to correlate the penetration of foscarnet with specific defects (e.g., elevated protein) of the blood-brain barrier. The correlation with the stage of HIV disease suggests minor alterations of the blood-brain barrier, undetectable by routine analysis of CSF, during the course of the infection. They might be due to HIV or to medication effects. With many of our patients, intrathecal IgG synthesis mostly of polyclonal origin occurs frequently in HIV infection; sometimes specific IgG against HIV is detected, suggesting encephalitis due to HIV.

Our results clearly confirm that foscarnet penetrates the blood-brain barrier and suggest that the concentrations achieved in CSF are sufficient for inhibition of CMV replication, although CSF penetration after a single-dose administration as well as under steady-state conditions is highly variable among individuals. In vitro, wild-type isolates of CMV were inhibited by more than 90% at 270 μM foscarnet (33). Concentrations between 300 and 500 μM were shown to prevent the appearance of late antigen and the development of inclusion bodies (33). In addition, HIV replication in H9 human cell cultures could be prevented completely by foscarnet at 680 μM (17). However, it is yet unclear what amount of foscarnet determined in CSF reaches the site of infection in the brain.

On the basis of the penetration of foscarnet into the CSF, clinical studies of the treatment of CMV encephalitis should be performed. Foscarnet merits consideration for patients with HIV encephalitis as adjuvant therapy with zidovudine or dideoxyinosine, since HIV replication is significantly inhibited by foscarnet in vitro (4, 33) and in vivo (15).

On the other hand, ganciclovir [9-(1-3-dihydroxy-2-propoxymethyl)guanine], a guanosine analog, is an effective virustatic drug for CMV infection, but the few case reports available showed CSF penetration between 0 and 41% (11, 18); treatment of CMV infections in the CNS showed variable results (6, 14, 19, 21).

Foscarnet has been shown to be the drug of choice for the treatment of CMV infection in the CNS, because it pene-

trates into the CSF and reaches concentrations that inhibit CMV replication in vitro effectively. Experimental data on foscarnet kinetics in CSF will be published soon.

REFERENCES

1. **AIDS Ophthalmology Study Group.** 1992. Studies of Ocular Complications of AIDS Research Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. N. Engl. J. Med. **326:**213–220.
2. **Behar, R., C. Wiley, and J. A. McCutchan.** 1987. Cytomegalovirus polyradiculoneuropathy in acquired immune deficiency syndrome. Neurology **37:**557–561.
3. **Brockmeyer, N. H., U. R. Hengge, L. Mertins, R. Malessa, R. Steinmetz, and M. Goos.** Foscarnet treatment in various cytomegalovirus infections. J. Clin. Pharmacol. Ther. Toxicol., in press.
4. **Chrisp, P., and S. P. Clissold.** 1991. Foscarnet: a review of its antiretroviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. Drugs **41:**104–129.
5. **Cinque, P., A. Castagna, L. Vago, M. Brytting, A. Accordini, A. D'Arminio, A. Lazzarin, A. Linde, and B. Wahren.** 1992. Rapid diagnosis of cytomegalovirus encephalitis in AIDS patients by DNA amplification on cerebrospinal fluid. Oral presentation 016 at the 3rd European Conference on Clinical Aspects and Treatment of HIV Infection, Paris.
6. **Davis, C. L., S. Springmeyer, and B. J. Gmerek.** 1990. Central nervous system side effects of ganciclovir. N. Engl. J. Med. **322:**933–934.
7. **Delpeche, B., and F. Lichtblau.** 1972. Etude quantitative des immunoglobulines G et de l'albumine du liquide céphalo-rachidien. Clin. Chim. Acta **37:**15–23.
8. **Eidelberg, D., A. Sortel, H. Vogel, P. Walker, J. Kleefield, and C. S. Crumpacker.** 1986. Progressive polyradiculopathy in acquired immune deficiency syndrome. Neurology **36:**912–916.
9. **Emminger, C.** 1992. Personal communication.
10. **Fanning, M. M., S. E. Read, M. Benson, S. Vas, and A. Rachlis.** 1990. Foscarnet therapy of cytomegalovirus retinitis in AIDS. J. Acquired Immun. Defic. Syndr. **3:**472–479.
11. **Fletcher, C., R. Sawchuk, B. Chinnock, P. de Miranda, and H. H. Balfour, Jr.** 1986. Human pharmacokinetics of the antiviral drug DHPG. Clin. Pharmacol. Ther. **1:**281–286.
12. **Gaub, J., C. Pedersen, A. G. Poulsen, L. R. Mathiesen, and K. Ulrich.** 1987. The effect of foscarnet (phosphonoformate) on human immunodeficiency virus isolation T-cell subsets and lymphocyte function in AIDS patients. AIDS **1:**27–33.
13. **Gozlan, J., J. M. Salord, M. Baudrimont, and E. Roullet.** 1992. Detection of cytomegalovirus DNA in cerebrospinal fluid of AIDS patients with neurological disease. Poster 154 at the 3rd European Conference on Clinical Aspects and Treatment of HIV Infection, Paris.
14. **Gravelau, P., R. Perol, and A. Chapman.** 1989. Regression of cauda equina syndrome in AIDS patient being treated with ganciclovir. Lancet **ii:**511–512. (Letter.)
15. **Jacobson, M. A., C. van der Horst, D. M. Causey, M. Dehlinger, R. Hafner, and J. Mills.** 1991. In vivo additive antiretroviral effect of combined zidovudine and foscarnet therapy for human immunodeficiency virus infection (ACTG protocol 053). J. Infect. Dis. **163:**1219–1222.
16. **Koeppen, A. H., L. S. Lansing, S. K. Peng, and R. S. Smith.** 1981. Central nervous system vasculitis in cytomegalovirus infection. J. Neurol. Sci. **51:**395–410.
17. **Koshida, R., L. Vrang, G. Gilljam, J. Harmenberg, B. Öberg, and B. Wahren.** 1989. Inhibition of human immunodeficiency virus in vitro by combinations of 3′-azido-3′-deoxythymidine and foscarnet. Antimicrob. Agents Chemother. **33:**778–780.
18. **Laskin, O. L., D. M. Cederberg, J. Mills, L. J. Eron, and D. Mildvan.** 1987. Ganciclovir for the treatment and suppression of serious infections caused by cytomegalovirus. Am. J. Med. **83:**201–207.
19. **Masdeu, J. C., C. B. Small, L. Weiss, C. M. Elkin, and J. Llena.** 1988. Multifocal cytomegalovirus encephalitis in AIDS. Ann. Neurol. **23:**97–99.
20. **McKenzie, R., W. D. Travis, S. A. Dolan, S. Pittaluga, I. M. Feuerstein, J. Shelhamer, R. Yarchoan, and H. Masur.** 1991. The causes of death in patients with human immunodeficiency virus infection: a clinical and pathologic study with emphasis on the role of pulmonary disease. Medicine **70:**326–343.
21. **Miller, R., J. Storey, C. Greco, M. Gonzales, and M. Jacobson.** 1988. Subacute radiculopathy caused by cytomegalovirus in patients with AIDS. Neurology **38:**242.
22. **Morgello, S., E. S. Cho, S. Nielsen, O. Devinsky, and C. K. Petito.** 1987. Cytomegalovirus encephalitis in patients with acquired immunodeficiency syndrome. Hum. Pathol. **18:**289–297.
23. **Mouas, H., S. Fegueux, S. Lariven, E. Bouvet, and T. De Broucker.** 1992. CMV polyradiculopathy in AIDS patients. Poster 211 at the 3rd European Conference on Clinical Aspects and Treatment of HIV Infection, Paris.
24. **Myerson, D., R. C. Hackman, J. A. Nelson, D. C. Ward, and J. K. McDougall.** 1984. Widespread presence of histologically occult cytomegalovirus. Hum. Pathol. **15:**430–439.
25. **Pantoni, L., D. Inzitari, M. G. Colao, E. De Mayo, P. Marini, and F. Mazzota.** 1991. Cytomegalovirus encephalitis in a non-immunocompromised patient: CSF diagnosis by in situ hybridization cells. Acta Neurol. Scand. **84:**56–58.
26. **Pettersson, K. J., and L. Nordgren.** 1989. Determination of phosphonoformate (foscarnet) in biological fluids by ion-pair reversed-phase liquid chromatography. J. Chromatogr. **488:**447–455.
27. **Post, M. J. D., G. T. Hensley, J. B. Moskowitz, and M. Fischl.** 1986. Cytomegalic inclusion virus encephalitis in patients with AIDS: CT, clinical and pathologic correlation. Am. J. Roentgenol. **146:**1229–1234.
28. **Sissons, J. G. P., L. K. Borysiewicz, B. Rodegers, and D. Scott.** 1986. Cytomegalovirus—its cellular immunology and biology. Immunol. Today **7:**57–61.
29. **Sjövall, J., S. Bergdahl, G. Movin, S. Ogenstad, and M. Saarimäki.** 1989. Pharmacokinetics of foscarnet and distribution to cerebrospinal fluid after intravenous infusion in patients with human immunodeficiency virus infection. Antimicrob. Agents Chemother. **33:**1023–1031.
30. **Taburet, A.-M., C. Katlama, C. Blanshard, G. Zorza, D. Gazzard, E. Dohin, B. G. Gazzard, C. Frostegard, and E. Singlas.** 1992. Pharmacokinetics of foscarnet after twice-daily administrations for treatment of cytomegalovirus disease in AIDS patients. Antimicrob. Agents Chemother. **36:**1821–1824.
31. **Vinters, H. V., M. K. Kwok, H. W. Ho, K. H. Anders, U. Tomiyasu, W. L. Wolfson, and F. Robert.** 1989. Cytomegalovirus in the nervous system of patients with the acquired immune deficiency syndrome. Brain **112:**245–268.
32. **Wahren, B., and B. Öberg.** 1980. Reversible inhibition of cytomegalovirus replication by phosphonoformate. Intervirology **14:**7–15.
33. **Wilkes, M. S., J. C. Felix, A. H. Fortin, T. A. Godwin, and W. G. Thompson.** 1988. Value of necropsy in acquired immune deficiency syndrome. Lancet **ii:**85–88.
34. **Zorza, G., E. Dohin, A. M. Taburet, C. Katlama, J. O. Lernestedt, and E. Singlas.** 1991. Pharmacokinetics of foscarnet after repeated infusions of 90 mg/kg twice daily for 2 weeks. Poster at the VII International Conference on AIDS, Florence, Italy.