Treatment of Gastrointestinal Cytomegalovirus Infection with Twice-Daily Foscarnet: a Pilot Study of Safety, Efficacy, and Pharmacokinetics in Patients with AIDS

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Ten patients with AIDS and cytomegalovirus (CMV) gastrointestinal infection were included in an open-label study to evaluate the safety, efficacy, and pharmacokinetics of 90 mg of intravenous foscarnet/kg of body weight twice daily accompanied by (pre)hydration of 500 to 750 ml. Efficacy was documented endoscopically, while safety was evaluated clinically by patient reports and physical and laboratory observation. The pharmacokinetics of foscarnet were evaluated after the first dose and following approximately 20 days of therapy. Nine patients (90%) responded histopathologically, nine (90%) responded endoscopically, and nine (90%) responded symptomatically to foscarnet therapy. Adverse events resulted in discontinuance of medication in 1 patient. The mean maximal concentration was 621 $\mu$M following the first dose and 687 $\mu$M at steady state ($P = 0.11$). The apparent elimination rate constant and elimination half-life were not different between dose 1 and steady state. There were no significant changes in foscarnet excretion or renal clearance between dose 1 and steady state. The steady-state volume of distribution was 23.4 liters following the first dose and 19.0 liters at steady state ($P < 0.002$). Twice-daily foscarnet appeared to be safe and efficacious in the treatment of CMV gastrointestinal disease in this study, resulting in endoscopic or histologic improvement in 9 of the 10 (90%) patients. Minor changes in clearance and volume of distribution noted at steady state compared to single-dose administration are readily explained by study design, known information about foscarnet pharmacokinetics, and changes in body weight and creatinine clearance in the patients.

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that is responsible for a wide range of diseases affecting patients with AIDS. It is the most common opportunistic virus which infects this population. While the most common site of involvement by CMV is the retina, where it produces a progressive necrotizing retinitis, gastrointestinal infection occurs in approximately one-third of all patients with AIDS (8).

CMV disease in patients with AIDS portends poor chances of long-term survival, but these may be improved with treatment. Three drugs, ganciclovir, foscarnet, and cidovir, are approved by the Food and Drug Administration for the treatment of CMV infections. Overall experience in the treatment of gastrointestinal CMV disease is limited: the only large studies have involved ganciclovir. Foscarnet has been reported to be effective in the treatment of CMV gastrointestinal disease in newly infected patients and in patients who have relapsed after therapy with ganciclovir (7). In noncomparative trials (5, 12, 15) and one comparative trial (3) it has been shown to have an effectiveness of 70 to 90%, similar to that of ganciclovir. Foscarnet is typically administered at dosages of 60 to 90 mg/kg of body weight every 8 to 12 h. At these dosages, dose-limiting nephrotoxicity and renal wasting of electrolytes occurred in 10 to 23% of patients with various degrees of (pre)hydration (6).

This pilot study was undertaken to investigate the efficacy and safety of twice-daily doses of foscarnet in the treatment of CMV gastrointestinal disease. In addition, the pharmacokinetics of this dosing schedule was investigated.

MATERIALS AND METHODS

Subjects. The study population included outpatients with AIDS and symptomatic CMV disease of the upper or lower gastrointestinal tract. Disease was verified by its endoscopic appearance and pathologically by the presence of characteristic CMV inclusion bodies in biopsy samples. A total of 10 patients were enrolled, 5 with upper gastrointestinal disease and 5 with lower gastrointestinal disease. The upper gastrointestinal tract was considered to include the esophagus, the stomach, and the duodenum to the ligament of Treitz. The lower gastrointestinal tract included the cecum; the ascending, transverse, and descending colon; the sigmoid colon; and the rectum. If a patient had disease at both sites, the principal investigator determined the predominant infection site on which to base the evaluation.

To be included in the study, patients had to meet the following criteria. The patients had to be over 18 years old and to have AIDS as defined by the Centers for Disease Control and Prevention (pre-1993). They had to have a life expectancy of over 8 weeks and to have never previously received anti-CMV medication. They were required to have adequate renal function, defined as a measured creatinine clearance of at least 50 ml/min. Patients treated with other potentially nephrotoxic medications or other investigational drugs within 7 days of study entry were excluded. Patients receiving systemic acyclovir or ganciclovir were also excluded. The use of analgesics, antiarrhythmics, and antacids was carefully monitored throughout the study. To rule out other causes of gastrointestinal disease, stool was cultured for bacteria, examined for ova and parasites, and assayed for the toxin of Clostridium difficile. The first 10 patients meeting these criteria were enrolled in the study. All patients signed informed-consent forms before entering the study. Samples for pharmacokinetic testing were obtained while patients were in the hospital. The study was reviewed and approved by the institutional review board.

Drug administration. Foscarnet at a concentration of 24 mg/ml was administered via a central venous catheter, or the solution was diluted to 12 mg/ml with DSW or normal saline and administered through a peripheral line over a period of 2 h. A dosage of 90 mg/kg two times daily was utilized in patients with an...
estimated or measured creatinine clearance of over 1.6 ml/min/kg. Patients received 500 to 750 ml of saline prior to the first infusion and 500 to 750 ml of saline concurrent with each subsequent infusion. Patients with lower creatinine clearances received an adjusted dose, in proportion to the clearance. Patients were treated for 4 weeks with an option to continue treatment for up to 6 weeks if they were not completely healed.

Laboratory analysis. On day 1 and at steady state, i.e., on days 17 to 20 and before the week 3 endoscopy on day 21, blood samples were collected for determination of plasma foscarnet concentrations. Blood samples were collected predose, at 1.0, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, and 12 h following the first dose, and during one dosing interval at steady state. Blood was collected in heparinized tubes and centrifuged immediately to separate the plasma fraction. Plasma samples were maintained at −20°C until assayed by high-performance liquid chromatography. A portion of urine was collected from each patient prior to the first dose to rule out assay interferences. Urine was collected over a 12-h period following the first dose and following the same steady-state dosing interval in which the plasma samples were obtained, at about 3 weeks. The volume of urine collected during each timed interval was measured, and a 10-ml sample was frozen at −20°C for assay by high-performance liquid chromatography.

Foscarnet concentrations in urine and serum were determined by TSI Mason Laboratories, Worcester, Mass. The plasma assay utilized two standard curve ranges: 2.0 to 26.6 μM and 26.6 to 356 μM. Concentrations between the minimum detectable concentration (0.010 μM) and the minimum quantifiable concentration (2.00 μM) were reported as estimates. Concentrations greater than the highest standard were diluted twofold or more and then reassayed; the reported concentration reflected this dilution. The analytical precision (RSD) for quality control samples was 9.6% at a concentration of 34.3 μM, 5.5% at 172 μM, and 3.4% at 343 μM with the high-range standard curve. With the low-range standard curve, the precision (RSD) was 16.4% at 4.2 μM, 6.3% at 16.8 μM, and 5.6% at 25.2 μM.

The urine assay utilized two standard curves: 2.0 to 26.6 μM and 26.6 to 356 μM. However, due to the high levels of foscarnet present in the samples, they were all analyzed by the high-range procedure, and the few samples which were below the high-range curve were reported as estimates. The minimum quantifiable level and minimum detectable level were 27 and 1.4 μM, respectively. The analytical precision (RSD) for urine quality control samples was 9.0% at 33.7 μM, 2.5% at 169 μM, and 1.5% at 337 μM.

Pharmacokinetic analysis. Data for pharmacokinetic analysis were available following the first dose and during one steady-state dosing interval, between days 17 and 21. A noncompartmental method was utilized in which the area under the plasma concentration curve (AUC) was determined with the linear trapezoidal rule for time zero to 12 h after the start of the intermittent infusion. The terminal elimination rate constant (λz) was estimated by weighted nonlinear regression (PCNONLIN version 3.0) from concentrations obtained between 6 and 12 h after administration of the dose. The model included monoexponential decay with proportional variance error. λo was utilized to calculate AUC from 0 h to ∞ (AUC∞) for dose 1. Total body clearance (CLt) was determined as the dose administered divided by either the AUC∞ following either the steady-state doses or the dose administered divided by the average renal clearance of foscarnet. Renal clearance was determined as the amount excreted in one dosing interval divided by the AUC of the drug for the same time interval. The exponential elimination rate constant (λz) is determined by the linear trapezoidal rule, AUC∞ is the estimated AUC of C(t) versus t by the trapezoidal rule, and T is the time of infusion. The same equations were used for the steady state, except that the amount of preexisting drug, estimated from the predose drug concentration, was decayed from the profile, assuming a first-order elimination rate and superposition principle. Two accumulation ratios were determined: the measured accumulation ratio (determined as the AUC0–12 at steady state divided by the estimated AUC of the gastrointestinal mucosa was graded on a scale of 0 to III as follows: 0, normal-appearing mucosa without inflammation or ulceration; I, mild inflammation or friability; II, severe inflammation; and III, ulceration of the mucosa.

The amount of foscarnet recovered in the urine for one dosing interval following the first dose and at steady state was determined. This amount was used to determine the percentage of the foscarnet dose excreted and the average renal clearances of foscarnet. Renal clearance was determined as the amount excreted in one dosing interval divided by the AUC of the drug for the same time interval.

Differences in pharmacokinetic parameters at steady state and after the first dose were evaluated by using a paired t test with a p value equal to 0.05. All data were summarized as means ± standard deviations (SD).

Blood was analyzed for complete blood count, electrolytes, and liver function at baseline on days 4 and 7 and then weekly until the sixth week of the study.

Definitions. Patients were asked to keep a daily diary of all adverse events that occurred over the study period for determination of their relationship to the study drug and were asked weekly to grade the severity of their symptoms. Endoscopy was performed at baseline and at either 3 or 6 months, depending on whether the patient's symptoms appeared to have resolved. The gross appearance of the gastrointestinal mucosa was graded on a scale of 0 to 3 as follows: 0, normal-appearing mucosa without inflammation or ulceration; I, mild inflammation or friability; II, severe inflammation; and III, ulceration of the mucosa.

Biopsy of the most involved area of the mucosa as well as uninvolved areas was performed. After biopsy, specimens were fixed in 15% unbuffered saline and stained with hematoxylin and eosin. All sections were examined assiduously in a blinded fashion by an experienced pathologist. Immunoperoxidase was used only if doubt about the presence of CMV existed.

Grading of CMV inclusions was done by the method of Rotterdam et al. (13) as follows: 0, no CMV inclusions per biopsy specimen; 1, 1 to 4 CMV inclusions; II, 5 to 9 CMV inclusions; and III, more than 10 inclusions. All mucosal biopsy samples revealing CMV inclusions also contained inflammatory infiltrates.

Response for upper gastrointestinal disease. A partial clinical response was defined as a 50% resolution of retrosternal pain, odynophagia, dysphagia, nausea, vomiting, or epigastric pain. A complete response was defined as 100% resolution of symptoms. Endoscopic or pathological response was defined as a decrease of gross inflammation by at least one grade or a decrease of inclusion disease by one grade after 3 or 6 weeks.

Response for lower gastrointestinal disease. A partial clinical response was defined as a 50% resolution of cramping abdominal pain, a reduction of diarrhea, an improvement of stool consistency, and disappearance of blood from the stool. A complete response was defined as 100% resolution of symptoms. Endoscopic or pathological response was defined as for upper gastrointestinal disease.

RESULTS

Patient characteristics. Ten human immunodeficiency virus (HIV)-infected homosexual men with CMV gastrointestinal disease were enrolled in the study. Table 1 shows demographic characteristics of the patients. Their age (mean ± SD) was 41 ± 3.9 years (range, 34 to 45 years). The mean peripheral CD4 cell count (mean ± SD) was 30.5 ± 23.4/mm³ (range, 4 to 64/mm³) in patients with CD4 counts available (8 of 10). All patients fulfilled the Centers for Disease Control and Prevention pre-1993 criteria for AIDS (4). The diagnosis of AIDS had been made 4.2 ± 6.2 months (mean ± SD; range, 0.4 to 18 months) before study entry. The AIDS-defining diagnosis was CMV infection in five of these patients, Kaposi’s sarcoma in four, and Pneumocystis carinii pneumonia in one. Five patients presented with CMV upper gastrointestinal disease, four presented with esophagitis, and one presented with gastritis. Five patients presented with CMV lower gastrointestinal disease, four presented with colitis alone, and one presented with both colitis and sigmoiditis. Some patients also had other conditions that are complications of AIDS, including Kaposi’s sarcoma (three patients) and P. carinii pneumonia in two patients. Although all patients took concomitant medications, none of the drugs was considered to affect the efficacy parameters. Table 2 shows the use of analgesics, anti diarrheals, and antacids both prior to and during the study. In many cases, single doses were given.

TABLE 1. Demographic information for AIDS patients at the beginning of twice-daily foscarnet therapya

<table>
<thead>
<tr>
<th>Patient (age [yr])</th>
<th>Duration of AIDS (mo)</th>
<th>Duration of gastrointestinal CMV (mo)</th>
<th>CD4 cell count (cells/mm³)</th>
<th>Site of CMV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (41)</td>
<td>0.4</td>
<td>0</td>
<td>64</td>
<td>Esophagus</td>
</tr>
<tr>
<td>2 (45)</td>
<td>8.5</td>
<td>0.4</td>
<td>14</td>
<td>Stomach</td>
</tr>
<tr>
<td>3 (44)</td>
<td>0.8</td>
<td>0.8</td>
<td>4</td>
<td>Esophagus</td>
</tr>
<tr>
<td>4 (44)</td>
<td>11.3</td>
<td>0</td>
<td>18</td>
<td>Esophagus</td>
</tr>
<tr>
<td>5 (34)</td>
<td>0.6</td>
<td>0.6</td>
<td>7</td>
<td>Colon</td>
</tr>
<tr>
<td>6 (36)</td>
<td>0.6</td>
<td>0.6</td>
<td>60</td>
<td>Colon</td>
</tr>
<tr>
<td>7 (43)</td>
<td>0.5</td>
<td>0</td>
<td>42</td>
<td>Colon</td>
</tr>
<tr>
<td>8 (45)</td>
<td>0.6</td>
<td>0.6</td>
<td>NA</td>
<td>Colon</td>
</tr>
<tr>
<td>9 (45)</td>
<td>0.6</td>
<td>0.6</td>
<td>35</td>
<td>Esophagus</td>
</tr>
<tr>
<td>10 (37)</td>
<td>18</td>
<td>0</td>
<td>NA</td>
<td>Colon</td>
</tr>
</tbody>
</table>

a All patients were male and Caucasian (except patient 9, who was Asian), and the risk factor for HIV seroconversion in all patients was homosexuality.

b NA, not available.
Response to treatment. Nine of the 10 patients (90%) responded histopathologically to therapy with twice-daily doses of foscarnet. The mean histopathological grade was 1.7 before treatment and 0.3 after treatment (Table 3). Three patients began therapy with grade III disease, one began with grade II disease, and six began with grade I disease. The one patient who started with grade II disease remained at grade II disease after 6 weeks of therapy, and one patient who began therapy with grade I disease failed histopathologically, having grade II disease after 3 weeks. This patient experienced only partial resolution of symptoms. The remaining patients (80%) ended with histopathological grade 0 disease.

Nine of the 10 (90%) patients responded endoscopically to treatment with foscarnet twice a day. The mean endoscopic grade was 2.5 before treatment and 0.4 after treatment (Table 3). Seven patients began therapy with grade III disease, one began with grade II disease, and two began with grade I disease. The patient who began with grade II disease ended with grade I disease, and one patient who began with an ulcerated (grade III) mucosa ended therapy unchanged (grade III). This patient had both histopathologic improvement and resolution of symptoms. The other eight patients ended therapy with grade 0 disease. Full resolution of symptoms occurred in eight patients, partial resolution occurred in one, and no improvement occurred in one. The patient whose symptoms failed to respond fully to twice-daily doses of foscarnet (patient 4) experienced severe hypokalemia and an increased creatinine concentration, necessitating discontinuation of foscarnet after 3 weeks. While the baseline examination revealed an ulcerated esophageal mucosa (grade III) with grade I histopathological disease, the mucosa appeared to be normal (grade 0) after 3 weeks but had grade II histopathologic disease. This patient continued to complain of nausea and vomiting, though retrosternal pain and odynophagia had resolved. Patient 10 experienced continued severe cramping abdominal pain, associated with four liquid stools per day, which was unchanged from his baseline symptoms despite endoscopic and histopathologic improvement of his CMV colitis after 6 weeks of therapy. Eight of the 10 patients (80%) gained an average of 3.8 kg over the study period, while two patients, including patient 4, for whom therapy failed, lost an average of 2.9 kg.

Adverse events. Adverse events associated with foscarnet therapy resulted in discontinuance of foscarnet in one patient who had hypokalemia and a decreased creatinine clearance. The other patients experienced little alteration in foscarnet dosing due to renal problems. Over the study period seven patients had their foscarnet dose changed because of a change in body weight and/or a change in measured creatinine clearance. For only two patients was the dose decreased due to a decrease in creatinine clearance, including the patient who required study discontinuation. The dose of foscarnet was increased in one patient due to an improvement in renal function. The remaining dosage changes were due to weight gain. All other adverse events, including dysesthesia at the site of intravenous administration (two patients), headache (two patients), pruritus, stomach pain, and increased weight, were mild and had no effect on therapy. Mild edema due to overhydration was noted in 2 of the 10 patients (20%) but was resolved with diuretics.

Pharmacokinetic analysis. Figure 1 shows the mean concentrations of foscarnet in plasma following the first dose and at...
TABLE 4. Plasma pharmacokinetic parameters for foscarnet

<table>
<thead>
<tr>
<th>Dose</th>
<th>Amt (mg)</th>
<th>C_max (µM)</th>
<th>AUC* (µM·h)</th>
<th>t1/2 (h)</th>
<th>CL (liters/h)</th>
<th>Vss (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5,316 ± 1,161</td>
<td>621 ± 130</td>
<td>2,537 ± 489</td>
<td>3.13 ± 0.681</td>
<td>7.07 ± 1.48</td>
<td>23.4 ± 3.10</td>
</tr>
<tr>
<td>Steady state</td>
<td>5,599 ± 866 (0.12)</td>
<td>687 ± 141 (0.11)</td>
<td>3,027 ± 771* (0.005)</td>
<td>3.41 ± 0.298 (0.34)</td>
<td>6.31 ± 0.946 (0.054)</td>
<td>19.0 ± 2.48 (&lt;0.002)</td>
</tr>
</tbody>
</table>

* Foscarnet was administered at 90 mg/kg every 12 h as a 2-h infusion. Data are presented for the first dose and dosing at steady state, i.e., following 17 to 21 days of treatment, and are means ± SD. The dose was adjusted for changes in renal function or body weight during the study. Numbers in parentheses are the P values for comparisons between dose 1 and steady state in the same column. 
† C_max: maximum concentration of drug in plasma.  
‡ t1/2: half-life.  
§ AUC[t→∞].  

steady state. The coefficients of variation for concentrations in plasma at measured time intervals were similar following single and multiple dosing, ranging from 17 to 49%. Four of the 10 patients during the steady-state assessment exhibited increases in concentrations in plasma at 12 h, which suggested that there had been premature initiation of the previous foscarnet infusion. Predicted 12-h concentrations from the regression of the terminal slope were used for these four individuals. The mean amount for the first dose of foscarnet was 5,316 mg (85 mg/kg; range, 58 to 92 mg/kg). Some subjects required dose adjustments due to changes in body weight or creatinine clearance. At the steady-state assessment, the mean dose was 5,599 mg, which was not statistically significantly different from the first dose (P = 0.120).

The AUC[t→∞] was only 6.6% greater than the AUC from 0 h to the end of the dosing interval (AUC[0→t]) on average. Thus, more than 90% of the AUC was based on concentration measurements. The R² for the regression of ln C(t) versus t (terminal slope) ranged from 0.886 to 1.00 (mean, 0.962). The mean pharmacokinetic parameters are provided in Table 4. The mean maximal concentration was 621 µM following the first dose and 687 µM at steady state (P = 0.11). Based on the estimated terminal elimination rate for dose 1, the AUC[t→∞] at steady state should exceed the AUC[0→t] for dose 1 by a factor of 1.18. The measured accumulation ratio, 1.27, was slightly higher; however, the difference between predicted and measured accumulation was not significant (P = 0.209). The total body clearance at steady state was 6.31 liters/h (105 ml/min), of which 72% was explained by renal clearance. The mean Vss was 19.0 liters, or approximately 0.3 liters/kg. Although there appeared to be a significantly higher Vss (P < 0.002) following the first dose, this difference may be an artifact of an imprecise estimation of λz. The AUC[0→t] at steady state was 3,027 µM·h, which corresponds to an average steady-state concentration of 252 µM during a steady-state dosing interval. The mean terminal elimination half-life was estimated as approximately 3.1 to 3.4 h.

The 12-h urine sample at steady state for patient 4 was not available for analysis. Approximately 71% ± 20% and 71% ± 23% (means ± SD) of the administered dose was excreted in the urine following the first dose and at steady state, respectively. The renal clearance (mean ± SD) was 5.34 ± 1.45 liters/h following the first dose and 4.58 liters/h at steady state. Thus, foscarnet appears to be excreted primarily by glomerular filtration with a small tubular secretion component. Neither the amount excreted (P = 0.838), percentage of dose excreted (P = 0.994), nor renal clearance (P = 0.190) differed between the first dose and steady state.

DISCUSSION

Treatment of gastrointestinal CMV infection with twice-daily doses of foscarnet is both safe and efficacious. This regimen resulted in endoscopic and histologic improvement after 3 to 6 weeks in 9 of 10 patients.

Although the quantity of foscarnet needed to inhibit clinical CMV isolates is quite variable, most viral strains are inhibited in vitro at tissue culture fluid concentrations of approximately 100 to 300 µM (1). The mean maximal concentrations in the patients evaluated in this study were 621 µM following the first dose and 687 µM at steady state. Foscarnet, at a dosage of 90 mg/kg twice daily, appears to achieve adequate steady-state concentration for inhibition of most CMV strains. The mean trough levels found in this study were lower than this threshold. Aweka et al. have shown that 60 mg of foscarnet/kg given thrice daily achieved mean peak and trough levels of 509 and 98 µM, respectively, after 3 days of therapy and 495 and 126 µM, respectively, after 14 days (2).

Twice-daily foscarnet therapy for CMV retinitis at a dose of 100 mg/kg has previously been compared with thrice-daily foscarnet therapy at a dose of 60 mg/kg (10). By the end of induction in this study, 97% of evaluable patients had responded to therapy, but there was no statistically significant difference in response between the groups undergoing the two dosing schedules. There was also no difference with regard to the time to respond to therapy, and there was a trend toward reductions in creatinine clearance and significantly decreased mean serum calcium concentrations in the thrice-daily treatment group. A similar positive response was noted in the present study. The 10 patients were relatively free from adverse effects. Treatment had to be discontinued for one patient (10%), and creatinine clearance was reduced in one other patient who was able to complete therapy. All other adverse effects were considered mild and did not result in alteration of the treatment course.

Patient 6’s colonic ulcer failed to resolve endoscopically after twice-daily treatment with foscarnet. Mucosal biopsy samples from this patient revealed no evidence of viral inclusions consistent with CMV disease, and symptoms resolved with therapy. Other etiologies of colonic ulcer should be considered in the case of this patient, despite our failure to identify other organisms in biopsy samples. One possibility is primary infection by HIV, which may be associated with colonic ulcers and inflammation with no other obvious opportunistic pathogens (9, 11). Given that he experienced symptomatic and histopathologic improvement and had gained 3.6 kg after treatment with foscarnet, therapy can be considered successful. Patient 4 had CMV esophagitis that failed to respond histopathologically. He did not experience full symptom resolution and had lost an additional 4.95 kg after foscarnet therapy was discontinued at the end of 3 weeks due to severely decreased creatinine clearance and severe hypokalemia. Although repeated endoscopy showed that this patient’s ulcer had resolved, CMV esophageal disease was probably still active.

This study confirms that foscarnet used as a twice-daily in-
fusion is an effective first-line therapy for CMV gastrointestinal disease, as effective as foscarnet thrice daily and ganciclovir have been shown to be for gastrointestinal disease. Foscarnet leads to resolution in 70 to 90% of patients when given three times a day, an efficacy that was matched by twice-daily therapy in this study. Thrice-daily therapy is also effective in the treatment of CMV gastrointestinal disease in patients in whom ganciclovir therapy has failed (7). Whether twice-daily dosing will also be effective after failure of ganciclovir therapy requires further evaluation.

As reported previously, the disposition of foscarnet appears to be triphasic, with mean half-lives of 0.45, 3.3, and 18 h (2, 14). This study was not designed to characterize either the distribution phase or the long terminal elimination phase, both of which were described previously. In this study, the mean half-lives were found to be 3.13 and 3.41 h following the single and multiple doses, respectively, which are consistent with the 3.3 h previously reported. Characterization of the terminal half-life would require blood sampling for more than 3 days after the final foscarnet dose. Mean concentrations following steady-state dosing increased to less than 30% higher than after the final foscarnet dose. We observed a mean $V_{ss}$ of 0.3 liters/kg that was considerably lower than that previously reported. Sjovall et al. (14) reported a mean $V_{ss}$ of 0.52 liters/kg (range, 0.28 to 0.74 liters/kg) based on a two-compartment model and 1.29 liters/kg (range, 1.04 to 1.67 liters/kg) based on a three-compartment model. The two-compartment model analysis was more reflective of the analysis method used in this study. Differences between the studies may be due to methodologic differences (compartmental versus noncompartmental analysis) and/or differences between patient populations. A reported volume of distribution phase or the long terminal elimination phase, both