Aweeka *et al.* (1989). It is not surprising that foscarnet pharmacokinetic variables are altered by changes in kidney function (Table 219.10).

Studies in cell-free systems have shown that foscarnet is not bound significantly to human plasma proteins, with binding of only 14–17% at concentrations from 1 to 1000 μM (Clinigen Healthcare, 2014).

## 5b. Drug distribution

Although the pattern of deposition of foscarnet in humans has not been studied, it is clear from studies in mice and from human pharmacokinetic studies that a significant proportion of the dose of foscarnet accumulates in bone and cartilage. In mice, approximately 30% of foscarnet is retained in these tissues (Helgstrand *et al.*, 1978). Extrapolating from elimination and clearance values in humans, it would appear that up to 22% of a dose is taken up into bone (Wagstaff and Bryson, 1994).

The steady-state volume of distribution in patients receiving 90 mg/kg twice daily or 60 mg/kg three times daily was 0.34–2 l/kg, with a mean of 0.74 l/kg (Aweeka *et al.*, 1989; Taburet *et al.*, 1992); the figures were similar in another study, although the body weights of the patients were not given (Dieterich *et al.*, 1997).

The diffusion of foscarnet into CSF has been examined in 27 HIV-infected patients receiving intravenous foscarnet at various dosages. The median cerebrospinal fluid (CSF) concentration of foscarnet was 80 μM, with a median CSF to plasma ratio of 0.27 (Raffi *et al.*, 1993). A separate study in which 26 patients were given a single 90 mg/kg intravenous infusion of foscarnet resulted in a mean CSF to plasma ratio of 0.23 ± 0.16 (Hengge *et al.*, 1993).

## 5c. Clinically important pharmacokinetic and pharmacodynamic features

Balfour and colleagues (1996) compared four different doses of foscarnet with no therapy in HIV-infected patients with asymptomatic CMV or HIV viremia (Table 219.11). A total of 27 subjects who had received a median of 22 months of single or combination nucleoside antiretroviral therapy were enrolled; they had median CD4 counts of 20/μl (range: 1–89); Effects on CMV viremia were assessed by end point dilution microcultures, CMV pp65 antigenemia, and CMV DNA concentrations in peripheral blood leukocytes; effects on HIV-1 viremia were quantified by end point cell dilution microculture, serum p24 antigen assay, and HIV viral load. A total of 22 subjects were given intravenous foscarnet for 10 days at 15 mg/kg every 8 hours, 30 mg/kg every 8 hours, 45 mg/kg every 12 hours, and 90 mg/kg every 12 hours, or were untreated. The effect of foscarnet on CMV antigenemia correlated well with foscarnet $C_{max}$, as well as with the foscarnet daily dose and area-under-the-concentration-time curve (AUC); HIV viral load did as well (Table 219.11). The data also suggested that dosing every 8 hours (at lower foscarnet total doses) was better than every 12 hours; effects on HIV viral load were similar (Balfour *et al.*, 1996).

A dose-ranging study showed that increasing the foscarnet dose increased the time to relapse of CMV retinitis in HIV-infected patients who very likely were receiving inadequate antiretroviral therapy (Jacobson, 1992a). In patients receiving 120 mg/kg/day time to relapse was more than 123 days, whereas in those receiving 90 mg/kg/day it was 95 days, and with 60 mg/kg/day, 90 days. A second study of 32 HIV-infected patients with previously untreated CMV retinitis showed that foscarnet maintenance doses of 120mg/kg/day resulted in a longer time before the retinitis progressed than doses of 90mg/kg/day (mean time before progression of retinitis of 336 and 157 days, respectively) (Jacobson *et al.*, 1993). These patients also were not receiving effective combination antiretroviral therapy. These trends were confirmed by a more detailed, retrospective analysis in which progression CMV retinitis progression rates were determined by comparisons of baseline and followup retinal photographs (Holland *et al.*, 1995). However, a further study by Jacobson and co-workers (1994) showed no difference in survival or time to retinitis progression in 156 patients with previously treated CMV retinitis who received 60, 90, or 120 mg/kg foscarnet per day as maintenance therapy.

Drusano and colleagues (1996) studied the pharmacodynamics of foscarnet in HIV-infected patients with CMV retinitis who were given varying doses of maintenance foscarnet (60–120 mg/kg once daily). These patients were also unlikely

Table 219.11. Foscarnet pharmacodynamics: effects of varying doses of foscarnet on the response to CMV and HIV infections.

| | | Median percent change from baseline in the assays used | | | | | |
|---|---|---|---|---|---|---|---|
| | | Dosed every 8 hours[a] | | Dosed every 12 hours[a] | | | |
| Virus | Assay used | 15 mg/kg (*n* = 4) | 30 mg/kg (*n* = 4) | 45 mg/kg (*n* = 5) | 90 mg/kg (*n* = 4) | All subjects | Untreated |
| CMV | DNA (viral load) | −98 | −97 | −96 | −72 | −85 | +383 |
| | Microculture | −83 | −96 | −98 | −99 | −93 | +55 |
| HIV | RNA (viral load) | −12 | −1 | −21 | −13 | −13 | +55 |
| | p24 antigen | −32 | −49 | −25 | −56 | −39 | +7.1 |

[a]All subjects were treated for 10 days.
*Abbreviation*: CMV: cytomegalovirus.
*Source*: Data from Balfour *et al.* (1996).