Table 219.12. Foscarnet pharmacodynamics: dose-ranging study of foscarnet prophylaxis of CMV infections following allogeneic bone marrow transplantation.

Group	Induction dose (mg/kg/day)	Maintenance dose (mg/kg/day)	CMV antigenemia after transplantation	
			% Antigenemic	No. of subjects
1	60	30	80	5
2	120	60	50	4
3	120	90	60	5
4	120	120	18	6

Abbreviation: CMV: cytomegalovirus.
Source: Reproduced with permission from Bregante *et al.* (2000).

to be taking effective, combination antiretroviral therapy The end point of the study was time to progression of CMV retinitis in relation to dose and foscarnet AUC. The AUC varied widely among patients, but higher AUCs increased the interval before retinitis relapsed. The presence of CMV viremia was a bad prognostic sign and was a prime determinant of a shorter period before retinitis relapsed (Drusano *et al.,* 1996). Bregante and colleagues (2000) assessed different induction and maintenance doses in allogenic bone marrow subjects with CMV infections for efficacy (Table 219.12). In this population, the best efficacy was doses of 120 mg/kg/day for both induction and maintenance.

INFANTS AND CHILDREN

There are no data on the pharmacokinetics or pharmacodynamics of foscarnet in neonates, infants, or children, although the drug has been used in a moderate number of children.

Two published case reports provide data on dosing foscarnet treatment in infants (Marei *et al.,* 2015; Nigro *et al.,* 2004). Nigro and colleagues (2004) successfully treated an infant with congenital CMV infection and resulting liver fibrosis with foscarnet, 60 mg/kg given three times daily for 3 weeks followed by 100 mg/kg three times a week for 3 months. At 2 months after cessation of treatment the child's liver was free of CMV DNA by PCR, and 10 years later the child had normal hepatic and neurologic function. Knorr and colleagues (2007) reported a 24-week premature baby who presented with CMV-related hematophagocytic lymphohistiocytosis on the 8th day of life. Treatment with granulocyte colony-stimulating factor and ganciclovir for 3 weeks was unsuccessful, and the child was switched to foscarnet, 100 mg/kg/day with methylprednisone. Within a week the neutrophil and platelet counts began to rise and they normalized after 3 weeks of foscarnet therapy, which was free of any side effects. At 18 months age the child was reviewed and was normal.

OCULAR PHARMACOLOGY

Intravitreal foscarnet pharmacokinetics has been studied (Diaz-Llopis *et al.*, 1994). After intravitreal injection of 2.4 mg foscarnet in two patients, the reported levels of foscarnet in vitreous were 896 and 75 μM at approximately 23 and 43 hours postinjection (Diaz-Llopis *et al.*, 1994). In a larger study in which vitreous samples were obtained from 60 eyes (52 patients), the mean concentrations of foscarnet in the vitreous of patients receiving induction or maintenance therapy by intravitreal injection were 189 ± 177 and 163 ± 167 μM, respectively; the mean vitreous to plasma ratio was 1.43 (Arevalo *et al.*, 1995).

The pharmacokinetics of intravitreal foscarnet was studied in rabbits by López-Cortés *et al.* (2000). After an intravitreal dose of 1 mg of foscarnet, foscarnet concentrations in the retina were about a quarter of those in the vitreous. One hour after administration, mean foscarnet concentrations in the vitreous and retina were 944 and 217 μg/g fluid or tissue, respectively, decreasing to 74 and 17 μg/g at 72 hours after injection. Within 26 hours, levels of foscarnet had fallen below the EC_{50} for most strains of CMV; in contrast, intravitreal ganciclovir levels remained above the EC_{50} for more than 60 hours (Figure 219.2). In another study, a single intravenous dose of foscarnet (120 mg/kg) in rabbits resulted in retinal levels higher than vitreous levels (Loépez-Cortés *et al.*, 2001).

Claro *et al.* (2009) studied the pharmacokinetics of intravitreal foscarnet in rabbits (as a solution and encapsulated in liposomes, and not available for treatment of humans). Compared with foscarnet solution, liposomal foscarnet achieved therapeutic levels in the retina for over 72 hours, far longer than foscarnet solution, while also reaching the vitreous humor with adequate levels to treat CMV infection (see Table 219.13).

5d. Excretion

Foscarnet is not significantly metabolized and is primarily excreted unchanged in urine, probably solely by glomerular filtration (Sjovall *et al.*, 1988; Sjovall *et al.*, 1989). A study by Noormohamed *et al.* (1997) showed that foscarnet was not secreted by renal tubular epithelial cells, as had been previously thought because its clearance was not retarded by probenecid; the authors concluded that foscarnet was eliminated only by glomerular filtration.

Plasma clearance of foscarnet after intravenous administration was 130–160 ml/minute, whereas renal clearance was approximately 90 ml/minute (Taburet *et al.*, 1992). In another study (Aweeka *et al.*, 1989), plasma clearance of foscarnet was similar, with a mean of 1.7–1.9 ml/min/kg (range: 0.9–3.6). Foscarnet has a long terminal-phase elimination half-life, which may be attributed to slow release from bone.

Aweeka and colleagues (1999) conducted a rigorous pharmacokinetic study of foscarnet in patients with normal renal function or varying degrees of renal insufficiency and those on hemodialysis. The mean plasma half-life of foscarnet was 1.9 hours in normal subjects and increased to 25 (± 19) hours in patients with renal failure not on dialysis. Foscarnet clearance by conventional hemodialysis averaged 183 ml/minute, increasing to 253 ml/minute during high-flux dialysis. A single round of dialysis by either method removed 37–38% of a single dose. A small study by Sam *et al.* (2000) showed