219

Foscarnet

John Mills and Suzanne M. Crowe

1. DESCRIPTION

Foscarnet, also known as phosphonoformate, usually abbreviated as FOS and occasionally abbreviated as PFA, is an organic analog of inorganic pyrophosphate. Foscarnet is a broad inhibitor of viral DNA polymerases, including both DNA-dependent and RNA-dependent enzymes (the latter usually termed reverse transcriptases). Consequently it is active against DNA viruses, including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and human herpesviruses types 6 and possibly 8 (HHV-6 and HHV-8) (Helgstrand *et al.*, 1978; Mesri *et al.*, 1996; Wagstaff and Bryson, 1994). In addition, it inhibits the reverse transcriptases of hepadnaviruses, including human and duck hepatitis B viruses, and primate immunodeficiency viruses such as HIV-1 and HIV-2 (Sandstrom *et al.*, 1985; Sarin *et al.*, 1985). It also interferes with mRNA synthesis of influenza viruses (Stridh *et al.*, 1979; Oberg, 1983; Strid *et al.*, 1989). Clinically, it is used to treat herpesvirus infections, especially those resistant to the usual antiviral drugs and, almost never, for treatment of multidrug-resistant HIV infection.

The chemical name for foscarnet is trisodium phosphonoformate hexahydrate, and it is marketed in solution by Clinigen Healthcare Ltd. under the brand name Foscavir (foscarnet solution). The molecular weight of foscarnet is 300.1 (1 μM = 0.3 μg/ml) and the chemical structure is shown in Figure 219.1.

Foscarnet is available for intravenous injection in water, pH 7.4, with 24 mg of trisodium phosphonoformate hexahydrate per milliliter (Foscavir injection); it is dispensed in 500-ml glass bottles (each milliliter of the pH 7.4 solution contains 24 mg or 80 μM of foscarnet).

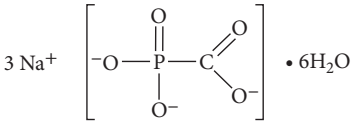

Figure 219.1. Chemical structure of foscarnet.

Prodrugs of foscarnet have been synthesized in an effort to increase oral absorption and tolerability, but they have not been studied clinically (Mills and Wu, 2004; Shirokova *et al.*, 2004), and a liposomal preparation for intraocular use has been developed, but it also has not undergone clinical trials (Claro *et al.*, 2009). Russo and colleagues (2014) developed foscarnet–chitosan nanoparticles that released foscarnet in cell culture, inhibiting replication of CMV and not causing any cytotoxicity, but that foscarnet preparation also has not undergone any clinical trials. A scleral plug has been developed for treatment of CMV retinitis with foscarnet and ganciclovir (Peng *et al.*, 2010), but this too has not undergone clinical trials.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

As noted, foscarnet inhibits nearly all classes of human herpesviruses ,including HSV-1 and -2, VZV, CMV, EBV, HHV-6, and possibly HHV-8. It also inhibits primate immunodeficiency viruses (HIV-1 and -2), simian immunodeficiency virus (SIV), and human and duck hepatitis viruses (see Table 219.1).

CYTOMEGALOVIRUS

Foscarnet at 0.3–0.8 μM inhibited the DNA polymerase of cytomegalovirus (CMV) by 50% (Oberg, 1983; Eriksson and Schinazi, 1989). The 50% effective concentration (EC_{50}) of foscarnet required to inhibit replication of human CMV strain Ad-169 in cell culture was somewhat higher, 102–130 μM, and the EC_{50} increased with increasing multiplicity of infection (Wahren and Oberg, 1980; Manischewitz *et al.*, 1990). Others report lower EC_{50} concentrations, ranging from 6 to 55 μM when measured by inhibition of plaque formation or cytopathology using laboratory strains of CMV (Wahren and Oberg, 1980; Andrei *et al.*, 1991; Neyts *et al.*, 1991). For clinical isolates of CMV, the EC_{50} for inhibition of replication is in the range 108–270 μM, generally being 1.5- to 8-fold more resistant than the laboratory strains (Oberg, 1989;